Secretary's Advisory Committee on Genetics, Health, and Society

Public Consultation Draft Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests

For Public Comment from March 9 to May 15, 2009

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Note to the Public

The potential effects of patenting and licensing practices on genetic tests and patient access to testing were first identified as priority issues by the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) in 2004. In previous reports, SACGHS has identified other factors affecting the adequacy and availability of genetic tests, including coverage and reimbursement of genetic tests and services, and their oversight. SACGHS explored those issues in great depth and issued reports in 2006 and 2008 respectively.[1]

The Committee's predecessor, the Secretary's Advisory Committee on Genetic Testing (SACGT), which was chartered from 1998 to 2002, also had explored the issue of gene patenting and licensing and whether certain licensing practices were affecting access to beneficial genetic tests. In a November 17, 2000, letter to the Secretary of Health and Human Services (HHS), SACGT acknowledged that gene patents can be critical to the development and commercialization of gene-related products and services, but it also noted that certain gene patenting and licensing practices may be having adverse effects on accessibility to and the cost and quality of genetic tests. Based on an exploration of perspectives on the issue from Government, industry, academia, legal experts, clinicians, ethicists, and patient communities, SACGT concluded that further study of the potential effects should be carried out to determine whether certain patenting and licensing approaches may be a) having adverse effects on access to and the cost and quality of gene tests; b) deterring laboratories from offering tests beneficial to patients because of the use of certain licensing practices; c) affecting the training of specialists who offer genetic testing services or d) affecting the development of quality assurance programs. In an August 8, 2001, reply to SACGT, the Acting Principal Deputy Assistant Secretary for Health concurred with the need for additional data.

SACGHS activities in this area were deferred pending the related work of a study committee of the National Academy of Sciences that was asked by the National Institutes

[1] These reports are available at http://oba.od.nih.gov/SACGHS/sacghs_documents.html.

of Health (NIH) to study the granting and licensing of intellectual property rights on the discoveries relating to genetics and proteomics and the effects of these practices on research and innovation. In the fall of 2005, a pre-publication copy of the NAS committee's report, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health,*[2] was released.

In reviewing the NAS committee's report, SACGHS agreed with its general thrust—particularly the conclusion that although the evidence to date suggests that the number of difficulties created for researchers by human DNA and gene patenting is currently small, the complexity of the patent landscape is worrisome and may become "considerably more complex and burdensome over time."[3] SACGHS also noted the report's recommendation that Federal research funding agencies should continue their efforts to encourage the broad exchange of research tools and materials.

SACGHS also concluded that given that the NAS committee's focus was on the effects of intellectual property practices on innovation and research rather than on clinical issues, its work was of limited relevance to concerns about patient access effects. Only one of its recommendations, in fact, dealt with the clinical dimension, and this pertained to a concern about the barriers that patents and exclusive licensees might represent to the independent validation of test results—a quality control issue. SACGHS decided that more information was needed regarding the effects of gene patents and licenses on patient access to diagnostic and predictive genetic tests and the ability of medical providers to order such tests for patients.

In June 2006, SACGHS held an informational session on the topic of gene patents and decided to move forward with an in-depth study. SACGHS formed the Task Force on Gene Patents and Licensing Practices and Patient Access to Genetic Tests (Task Force)—composed of SACGHS members, nongovernmental experts appointed as ad hoc

[2] NRC. (2006). *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health.* Washington, DC: National Academies Press.
[3] Ibid., p. 3.

members, and technical experts from relevant Federal agencies—to guide the development of a report assessing whether gene patenting and licensing practices affected patient and clinical access to genetic tests, and if so, how. The Task Force decided to limit the scope of its inquiry to those genetic tests that rely on analysis of nucleic acid molecules to determine human genotype, whether used for diagnostic, predictive, or other clinical purposes. As such, the kinds of patent claims that the Committee evaluated were nucleic acid-related patent claims associated with genetic tests for human genotype. The report does not address protein-based genetic tests or protein-related patent claims associated with tests designed to infer genotype.

At its March 2007 meeting, the Committee received a primer on gene patents and licensing that provided the background necessary to understand key issues. In May 2007, the Task Force discussed next steps and planned an international roundtable, so that the full Committee could learn about the impact of gene patents and licensing practices in other countries and the strategies that are employed to minimize adverse effects to patient access.

The Task Force decided that if fact-finding and evidence-gathering efforts identified problems—or potential problems—in patient access, it would formulate recommendations to be forwarded to the full Committee for its consideration.

Debra G.B. Leonard, M.D., Ph.D., of New York Presbyterian Hospital, served as the first chair of the Task Force. At the conclusion of Dr. Leonard's SACGHS term, James P. Evans, M.D., Ph.D., of the University of North Carolina, was appointed to chair the group. The Task Force organized two roundtables—one focused on international issues in gene patenting and the other on general issues in patent law and policy—and it commissioned several studies, as described later in this report. The Task Force's draft report was presented to the full Committee for review in December 2008 in preparation for its release to the public for comment.

This draft report presents SACGHS'preliminary findings on the effects of patents covering genetic tests and related licensing practices and a range of policy options for consideration and comment by the public. The Committee has thought about the types of steps that might be taken in this area and presents them as a range of potential policy options for the purpose of gathering public perspectives. Public input about the need for change, the appropriateness, feasibility, and implications of the policy options presented, as well as any others the public might suggest, is needed before SACGHS will be ready to develop specific recommendations. SACGHS also encourages the public to provide any additional information and data regarding the positive or negative effects gene patenting or licensing practices have had, are having, or may have on patient and clinical access to genetic tests.

The Committee will carefully consider public input on these options in finalizing its report and developing and recommendations to the Secretary.

Comments received by May 15, 2009 will inform SACGHS in the preparation of the final report and recommendations that will be presented to the Secretary of HHS. To submit comments to SACGHS, please e-mail them to Darren Greninger, at greningerd@od.nih.gov. Alternatively, comments can be mailed to Mr. Greninger at the National Institutes of Health (NIH) Office of Biotechnology Activities, 6705 Rockledge Drive, Suite 700, Bethesda, MD 20892 (20817 for non-U.S. Postal Service mail), or faxed to 301-496-9839.

SACGHS looks forward to receiving the public's feedback on this draft report and potential policy options as well as additional relevant information. SACGHS appreciates public interest in its work on this issue.

About SACGHS

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) was first chartered in 2002 by the Secretary of the U.S. Department of Health and Human Services (HHS) as a public forum for deliberation on the broad range of policy issues raised by the development and use of genetic tests and, as warranted, to provide advice on these issues. Its mandate includes the following areas of study:

- Integration of genetic and genomic technologies into health care and public health
- Clinical, public health, ethical, economic, legal, and societal implications of genetic and genomic technologies and applications
- Opportunities and gaps in research and data collection and analysis efforts
- Impact of current patent policy and licensing practices on access to genetic and genomic technologies
- Uses of genetic information in education, employment, insurance, and law

SACGHS consists of up to 17 individuals from around the Nation who have expertise in disciplines relevant to genetics and genetic technologies. These disciplines include biomedical sciences, human genetics, health care delivery, evidence-based practice, public health, behavioral sciences, social sciences, health services research, health policy, health disparities, ethics, economics, law, health care financing, consumer issues, and other relevant fields. At least two of the members are specifically selected for their knowledge of consumer issues and concerns and of the views and perspectives of the general public.

Representatives of at least 19 Federal departments or agencies may also sit on SACGHS in an ex officio (nonvoting) capacity. The departments and agencies are the Department of Commerce, Department of Defense, Department of Education, Department of Energy, Administration for Children and Families (HHS), Agency for Healthcare Research and Quality (HHS), Centers for Disease Control and Prevention (HHS), Centers for Medicare

& Medicaid Services (HHS), Food and Drug Administration (HHS), Health Resources and Services Administration (HHS), National Institutes of Health (HHS), Office for Civil Rights (HHS), Office for Human Research Protections (HHS), Office of Public Health and Science (HHS), Department of Justice, Department of Labor, Department of Veterans Affairs, Equal Employment Opportunity Commission, and Federal Trade Commission.

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Chapter I

Introduction

The science and clinical applications of genetic testing have undergone great advances in recent decades. Originally, genetic testing emerged as a tool to evaluate a person's risk of developing or passing on single-gene disorders, enabling early detection of inherited diseases or conditions. However, advancing knowledge of the human genome—coupled with rapidly evolving technologies—is providing new opportunities to assess common, multifactorial disorders such as heart disease, diabetes, asthma, and mental illness, which likely involve multiple genes and environmental factors. Moreover, genetic testing increasingly is being developed for use in personalized medicine, for example, for targeted treatment selection, identification and quantification of treatment risks, monitoring of treatment effectiveness and prognosis, and personalized disease management. Thus, the number of tests being developed and used in clinical practice will increase over time.

In previous reports, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) has described the wide array of genetic tests currently in use, which rely on biochemical, cytogenetic, and molecular methods or a combination of these methods to analyze DNA, RNA, chromosomes, proteins, and certain metabolites.[4] The scope of this investigation and report, however, is on those genetic tests that rely on analysis of nucleic acid molecules to determine human genotype, whether used for diagnostic, predictive, or other clinical purposes. As such, the kinds of patent claims that the Committee evaluated were nucleic acid-related patent claims associated with genetic tests for human genotype. The report does not address protein-based genetic tests or protein-related patent claims associated with tests designed to infer genotype. Evolving intellectual property law and practice has both enabled and limited the patenting of matter and methods directly relevant to genetic tests, for example, patents on isolated nucleic acid molecules and patents covering diagnostic processes.

[4] In particular, see *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*.

The role of patents in spurring innovation and investment in biomedical research is widely recognized and supported. The U.S. Supreme Court has made it clear that genetically engineered organisms can qualify as patentable subject matter, and the U.S. Patent and Trademark Office has determined that nucleic acid molecules are patentable. However, there has been some controversy and debate about such patents and how broad they should be.[5] While the patent system is designed to encourage innovation by granting to inventors, for a limited period of time, the right to exclude others from making, using, or selling the patented invention, the system also can involve making trade-offs between providing an incentive for test development and the costs, if any, to society that can result from granting an inventor exclusive rights to the resulting invention. Patents have a utilitarian function in U.S. law and exist to promote a positive good—specifically, "progress in the sciences and useful arts".

In recent years, concerns have been raised that in the area of patented genetic tests, patenting and exclusive licensing practices might have limited the availability and quality of these tests.[6] For example, a laboratory may be prevented from or choose not to offer diagnostic tests because of actual or anticipated patent or license enforcement. Another concern is that where a genetic test is protected by a patent, one cannot "invent around" the patent to create an equivalent, but non-infringing test.[7] For example, if one wanted to create a genetic test and had to invent around a patent claiming a gene molecule, one might make a genetic test that detected the protein of the gene instead of the gene itself.

[5] See, for example, Cho, M.K., et al. (2003). Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnosis* 5(1):3-8

[6] See, for example: Eisenberg, R.S. (1989). Patents and the progress of science: Exclusive rights and experimental use. *University of Chicago Law Review* 56:1017-1086, p. 1025; Merz, J., Kriss, A., Leonard, D., and M. Cho. (2002). Diagnostic testing fails the test: The pitfalls of patents are illustrated by the case of haemochromatosis. *Nature* 415:577; Liddell, K., Hogarth, S., Melzer, D., and R.L. Zimmern. (2008). Patents as incentives for translational and evaluative research: The case of genetic tests and their improved clinical performance. *Intellectual Property Quarterly* 3:286-327; Paradise, J., Andrews, L., and T. Holbrook. (2005). Intellectual property. Patents on human genes: an analysis of scope and claims. *Science* 307(5715):1566-1567; Caulfield, T., Cook-Deegan, R.M., et al. (2006). Evidence and anecdotes: an analysis of human gene patenting controversies. *Nature Biotechnology* 24(9):1091-1094.

[7] Aymé, S. et. al. (2008). Patenting and licensing in genetic testing. *European Journal of Human Genetics* 16:S3-S9. See also Westin, L.P. (2002). Genetic Patents: Gatekeeper to the Promised Cures. *Thomas Jefferson Law Review* v.25.

Such a test might be useful, but it could not be fairly characterized as an equivalent test. The main difference is the protein test would only reveal presence of the gene when it is being expressed. The test based on the gene, on the other hand, would reveal the presence of the gene even if unexpressed.

Also concerning is the potential for "hold-out" issues in which, for example, a single entity holding critical technology may refuse to license or may charge what others regard as unfair or disproportional fees even though it holds only one technology of many needed for a clinically useful test. In such a case, no practical diagnostic test would be possible without the cooperation of the one controlling entity regardless of the patent and licensing status of the other genes. Thus, as testing increasingly involves multiplex technologies there is concern that mutual blocking situations and patent thickets may develop.[8]

In the realm of quality control and assurance of genetic tests, some members of the Task Force and individuals testifying during its meetings are concerned that exclusive licenses could affect the development of method validation and proficiency testing by peers, create a lack of diversity in analytical methods and test interpretation, thwart the development of confirmatory testing in a second laboratory for unusual cases, and possibly restrict access to testing for some patients. Could the inappropriate use of patents and licensing agreements impede improvements or upgrades to existing tests and make it impossible for clinicians to verify a particular test result—in effect, to get a second opinion—because the "confirmatory" test would have to be performed by the same laboratory, or company, that conducted the original test? Or, are these concerns—while possibly valid—more relevant to oversight of laboratory quality control than to patenting and licensing practices?

[8] Ayme, S., Matthijs, G., and S. Soini, on behalf of the ESHG Working Party on Patenting and Licensing. (2008). Patenting and licensing in genetic testing Recommendations of the European Society of Human Genetics. *European Journal of Human Genetics* 16:405-41; B. Verbeure, E. van Zimmeren, G. Matthijs, and G. Van Overwalle. (2006). Patent pools and diagnostic testing. *Trends in Biotechnology* 24(3):115-120.

Other concerns are more focused on the future. In some cases, the development and use of genetic technologies for clinical testing could involve multiple patents and require multiple licensing agreements with different patent holders. Such patent stacking complexities could act as a barrier to product development. For example, development of a multi-gene test could require the acquisition of a separate license for each patented gene. This is an especially salient problem in medical genetics given that "genetic heterogeneity" is the rule, in which mutations in many different genes can often result in identical phenotypes or disease states, making the testing of multiple genes a necessity in many clinical situations. Additional problems may arise when multiple patents apply to a single gene, requiring multiple licensing agreements that could potentially result in high costs for the diagnostic or screening panel analyzing mutations in a single gene. This problem could be amplified for tests screening numerous different genes in a single assay. [9]

Much of the policy discussion about these issues revolves around two cases in particular, testing for Canavan's disease and testing for *BRCA1/2* for breast cancer. The cases, described in greater detail in the next chapter, have led to policy changes, such as laws passed in France and Belgium specifically intended to prevent gene patents from blocking access to clinical genetic testing.

In the first case, the commercialization of a genetic test for Canavan disease has been cited as an example of how licensing practices can adversely affect the cost and accessibility of genetic tests. Miami Children's Hospital (MCH) initially obtained the patent on the gene responsible for Canavan disease and some methods for screening mutations in this gene. When MCH initially sought to license the patent, it issued licenses

[9] Multiple patents on a gene may occur when each mutation or form of the gene has its own patent or when a patent office has inadvertently issued several patents on the same gene/mutation. Estimates vary regarding how many multiple patent grants have been made; however, based on language imprecision, technology overlap, legal subtleties, and the absence of technical testing done by the world's patent offices, multiple patents are often issued on overlapping subject matter. Some estimates indicate that for less-well-known genes or those discovered by brute force, such as by the various genome projects, there may be as many as a dozen patents on a single gene or parts thereof. In some instances, inventors were not even aware of the function of their gene technology. USPTO resolved some of this through the issuance of the utility and written description examination guidelines in 2001.

that imposed limits on the number of tests that a laboratory could perform, penalties for any academic laboratory that exceeded the set capitation, and a royalty fee of $12.50 per test. Families affected by Canavan disease sued MCH over what they considered to be a restrictive licensing agreement and excessive royalties for the use of the genetic test. The families believed the licensing terms would limit the accessibility of genetic testing and felt that they had participated in the research effort to identify the gene involved in the disease and to benefit the public as a whole. The lawsuit was settled, with the agreed-upon licensing terms undisclosed but apparently satisfactory to the plaintiffs.

In the second case, intense controversy has surrounded restrictive licensing of *BRCA1* and *BRCA2*, two genes important in approximately 5 percent of breast cancer. Myriad Genetics, Inc., holds right to several patents covering these genes. Myriad offers diagnostic testing for samples from around the world and has licensed only a few other laboratories to perform the test. The complexity of the test is cited as one reason for restricting the number of laboratories performing the study to highly specialized reference laboratories such as Myriad. However, testing for *BRCA*1/2 mutations does not qualitatively differ from other sequence-based genetic testing. There are concerns that the cost of the licenses is keeping the cost of the test high and reducing access to the test itself and to the datasets being generated both in the United States and abroad. There are also some concerns raised about interference with research on breast cancer outcomes as they relate to *BRCA* status. In addition, some experts suggest that there may be alternative approaches to the analysis of the gene that may improve on Myriad's approach, but that cannot be explored because of the patent.

The case studies in this report outline the Canavan controversy in greater detail and examine whether concerns about Myriad's practices are founded.

Questions have been raised about whether problematic issues raised by cases such as these might be more widespread. Moreover, even if these concerns objectively reflect the social costs incurred from patenting and licensing practices, those costs must be weighed against the incentives that patents and licenses potentially provide for investment in the

research and development needed to provide new genetic tests. If patents could not be used to protect genetic tests, is there the risk that these tests would not be developed at all or that these tests would be developed in ways that do not meet the needs of patients?[10] Similarly, if patent holders did not have the option of exclusively licensing a patented genetic discovery for further development, is there the risk that some inventions would not be commercialized at all for the public?

Many of the concerns raised about the effects of gene patents on research and clinical care have been studied by American and international groups, including the National Research Council (NRC), the Nuffield Council, the Organisation for Economic Co-Operation and Development (OECD), and the Australian Law Reform Commission, as well as by numerous bioethicists (see the next chapter for further information). There is consensus that patents by and large have not prevented new research and that patent protection has indeed encouraged the huge investments that can be required to develop new therapies.[11] However these groups also have expressed caution regarding the potential for problems in the rapidly developing realm of genetic technologies, especially in the context of diagnostics. In 2002, the Nuffield Council recommended that U.S. and European patent authorities set more stringent standards for DNA patents and that "in the future, the granting of patents that assert rights over DNA sequences should become the exception rather than the norm."[12]

Likewise, the 2006 NRC report, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health,* concluded in part that "[f]or the time being, it appears that access to patented inventions or information inputs into biomedical research rarely imposes a significant burden for biomedical researchers."[13] Nonetheless, it cautioned that patent issues could become "considerably

[10] This is just one of the questions examined in this report.

[11] Aymé, S., Matthijs, G., and S. Soini. (2008). Patenting and licensing in genetic testing: Recommendations of the European Society of Human Genetics. *European Journal of Human Genetics* 16:S3-S9.

[12] Nuffield Council. (2002). *The Ethics of Patenting DNA.* London: Nuffield Council on Bioethics, p. 70.

[13] NRC, 2006, op. cit., p. 2.

more complex and burdensome over time,"[14] and it urged continuing efforts to promote free exchange of research materials and data and the creation of some mechanism to keep patent examiners up to date on new developments in their fields.

Thus, despite general agreement regarding the importance of patents for innovation in therapeutics and lack of evidence that patenting *per se*[15] poses a problem with access to DNA-based technology or the development of new technologies, there is persistent concern that some DNA-based patents may be too broad or obvious and that overly broad claims and/or restrictive licensing may be (or may be poised to) adversely affect public access to and use of these new inventions, especially in the context of diagnostics. Previous reports exploring the impact of intellectual property rights on genetic and genomic research have indicated that licensing practices play a critical role in researcher access. Although information about patents is publicly available, particularly in the United States and Europe, information about how individual patents are licensed is not publicly available, because most licensing agreements are considered to represent confidential business information.

Also of relevance are policies aimed at promoting the transfer of knowledge for public benefit, specifically with regard to federally funded or conducted research. The Federal Government supports a significant amount of biomedical research relevant to genetic tests. Two key pieces of legislation were enacted in 1980; one was designed to increase U.S. competitiveness and economic growth by promoting the transfer of inventions made with Government funding by Government grantees and contractors to the private sector for development into commercial products and services (the Patent and Trademark Amendments of 1980 [P.L. 96-517], also known as the Bayh-Dole Act); and the other authorized Federal agencies to transfer federally owned technology to the private sector for product development and authorized the use of cooperative research and development agreements between Federal laboratories and nonfederal entities (the Stevenson-Wydler

[14] Ibid., p. 3.
[15] Pressman L., et al. (2006). The licensing of DNA patents by U.S. academic institutions: an empirical survey. *Nature Biotechnology* 24:31-39.

Technology Transfer Act of 1980). These laws allowed government scientists and academic scientists using federal funds to file patents and receive royalties for their inventions. Because the public and academic sectors were conducting and continue to conduct a significant share of research relevant to genetic tests, policies regarding their patenting and licensing policies and practices also deserve scrutiny.

It is against this backdrop of history and debate that the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) undertook its examination of the issues surrounding DNA-based patents and genetic test development. Throughout its deliberations, SACGHS was fully aware that regulation of intellectual property rights may not necessarily be the optimal primary point of action for resolving all problems regarding clinical and patient access to genetic testing, testing quality or reimbursement issues. Rather, the Committee will continue to focus on reasonable policy recommendations that promise the greatest degree of benefit in promoting patient access while avoiding ancillary detrimental effects of such policies..

The following chapter describes the terminology adopted and methodology used by SACGHS in undertaking its task. That chapter is followed by the Committee's preliminary findings. A fourth chapter provides preliminary conclusions and a final chapter provides a range of policy options for consideration. A summary chapter will be prepared following the Committee's consideration of the public comments received.

Chapter II

Terminology, Study Questions, and Methods

Terminology

This report focuses on those patents related to health-related *genetic tests*, whether used for diagnostic, predictive, or other clinical purposes. As noted in Chapter I, the scope of this investigation and report is on those genetic tests that rely on analysis of nucleic acid molecules to determine human genotype, whether used for diagnostic, predictive, or other clinical purposes. As such, the kinds of patent claims that the Committee evaluated were nucleic acid-related patent claims associated with genetic tests for human genotype. The report does not address protein-based genetic tests or protein-related patent claims associated with tests designed to infer genotype. Indeed, there are many other types of genetic tests beyond the scope of this report.[16]

Information was gathered on both *clinical access* and *patient access* to such tests. *Clinical access* means a health care professional's ability to obtain or provide genetic tests for patients, which involves reimbursement and cost issues in addition to medical use of genetic information. *Patient access* means the ability of a patient to obtain needed genetic testing.

Although focused on genetic tests used in clinical practice, data collection efforts also considered effects on translational research, because the development and integration of

[16] In previous SACGHS reports, the Committee has defined a *genetic* or *genomic test* as an analysis of human chromosomes, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), genes, and/or gene products (e.g., enzymes and other types of proteins), which is predominately used to detect heritable or somatic mutations, genotypes, or phenotypes related to disease and health. Genetic or genomic tests detect inherited and somatic variations in the genome, transcriptome, and proteome. The tests can be used to analyze one or a few genes, many genes, or the entire genome. They can be used for disease diagnosis, prognosis, and prediction; carrier testing and screening; risk assessment; and clinical management, including drug response prediction. See, for example, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services.* In its discussions, the Task Force also considered patents on nonhuman genes that are involved in human disease (e.g., pathogenic genes) but the report does not address them.

new genetic knowledge and tests into clinical practice can also ultimately affect patient access.[17]

Research Questions

SACGH's data collection efforts were guided by the following key questions:

- **Patent Policy and Practice**. What role does U.S. patent policy play in clinical access to existing and developing genetic tests? How does the inventor's or patent owner's use, enforcement, and licensing of the patented genetic information affect clinical access? How does the legal interpretation of the patentability and patent boundaries affect clinical access to such technologies?

- **Licensing Policies and Practices**. Are licensing practices affecting clinical access to genetic information and tests? Are licensing practices affecting the ability of industry and academia to develop genetic tests? What role do technology transfer programs play in influencing clinical access to genetic tests?

- **Evidence**. What is the evidence for either positive or negative effects of gene patents and licensing practices on clinical and patient access to existing and developing genetic tests? Evidence may include, but is not limited to, studies showing direct correlation between the existence of one or more gene patents and access to the particular genetic tests, economic impact analyses, and comparisons between access to tests pre- and post-patenting. Other evidence might include anecdotal evidence from affected patients and health care providers. If there are barriers to patient access to genetic tests, where within the health care system do such barriers exist (e.g., development, procurement, reimbursement)? What elements of the patent system relate to these aspects of the health care system (e.g., patent application, patenting, use of/licensing, enforcement)?

[17] Patents on processes or technologies used in the sequencing of DNA or the identification of genes are not within the scope of this study.

- **Development and Translation Effects**. In what ways do gene patents and/or licensing and enforcement practices enhance or create incentives or barriers to the development, implementation, and continued performance of clinical genetic tests?
- **Cost of Tests**. What is the evidence of positive and negative effects of gene patents and licensing/enforcement practices on the cost and pricing of genetic tests? What are the economic data or studies that analyze the contribution of gene patents to the cost of genetic tests and ultimately to patient access and treatment outcomes?
- **Quality of Tests**. Is the quality of genetic testing affected by gene patents and licensing practices? Are gene patents and licensing practices affecting the ability to perform multiple gene tests, panels, and arrays?
- **Other Measures/Approaches**. What other measures and approaches can be employed to assess the direct effect of gene patents and licensing practices on patient access and treatment outcomes to genetic tests?

- **Alternative Models**. Are there feasible alternative models, perhaps from foreign nations, and innovations that could be applied to the patent and licensing system to enhance the benefits of the system? What are the lessons from parallel situations, in health care and other areas, in which patents have enhanced or restricted access to a technology?

Study Plan

A three-part study was undertaken to address these questions.

Part 1—Data Gathering and Analysis

Part 1 involved a literature review, the determination of acceptable proxies, consultations with experts, case studies to validate proxies, and additional research.

Literature Review. The literature review had two main objectives: 1) to identify what data, if any, exist regarding the positive and negative effects of gene patents and associated licensing/enforcement practices on clinical and/or patient access to genetic tests and 2) to identify data gaps and the measures that can be used to address these gaps or acceptable proxies that can be utilized when such measures do not exist. Specifically, the literature review was used to identify:

- empirical data on any positive or negative effects of gene patenting and associated licensing/enforcement practices on the availability of[18] and access to existing and developing genetic technologies and tests as well as data gaps in attributing the impact of patents on availability and access;
- case histories comparing patented and unpatented technologies, or technologies licensed in different ways, or particularly salient cases that have generated policy discussion;
- economic data or studies that analyze the contribution of gene patents to the cost of genetic tests and ultimately patient access (e.g., how companies set prices given the market environment, price to the patient, how intellectual property influences the market for genetic technologies, and factors that influence differential pricing);
- studies comparing economic and product development in countries with divergent patent systems and measuring the incentivizing or disincentivizing effects of patents on the development of new technologies;
- patent-related factors that lead to perturbations in established practice patterns (e.g., having to send samples to a single licensed service provider);
- factors, other than patent considerations, that influence the cost of a genetic test or technology, such as the negotiation of pricing for clinical services as well as health care reimbursement and procurement practices;

[18] *Availability* refers to the ability of parties to use a technology or product when they do not hold patent rights to that technology or product.

- current measures used to quantify the effect of patents and medical practice on access to genetic technologies and genetic tests in addition to any gaps in suitable ways in order to measure the impact of patents on genetic test availability and access;
- appropriate types of derivative statistics and data measures that can be used as proxies to address data gaps and an assessment of the feasibility of using such measures; and
- feasible alternative models that could be applied to the patenting and licensing system to enhance benefits or mitigate costs, and lessons from parallel situations in health care and other areas where patents have enhanced or restricted access to a technology.

Expert Consultations. Experts on gene patents and licensing practices as well as associated issues were identified and consulted through a roundtable. A discussion guide was developed that included questions about the best methodologies to use to assess gaps, cost-effectiveness, and potential organizations to complete such a study. The product of the consultations was a methodology for applying the measures to fill data gaps identified through the literature review.

Case Studies. In December 2006, SACGHS staff commissioned the Center for Genome Ethics, Law & Policy[19] housed within Duke University's Institute for Genome Sciences & Policy, to assist in carrying out components of the study, including case studies. The Center also conducted an analysis of patenting and licensing of genetic diagnostics and prepared a conceptual overview. The Center was selected because it received a Centers of Excellence award from the National Human Genome Research Institute Ethics, Legal, and Social Implications (ELSI) Research Program. The focus of the Duke Center's research is to gather and analyze information about the role of publication, data and materials sharing, patenting, database protection, and other practices that may affect the flow of information in genomics research.

The Center conducted eight case studies of 10 clinical conditions. The case studies were selected because they provided informative examples of genes that have been patented compared to others that have not, and they illuminated the ways in which such patents are licensed. The case studies were expected to allow some conclusions to be drawn about the extent to which gene patenting and licensing practices have affected patient access to patented genetic tests, either positively or negatively. Each case involves a Mendelian (inherited) disorder or a cluster of disorders associated with a clinical syndrome for which genetic tests are available. The case studies focused on:

1. inherited susceptibility to breast/ovarian cancer and colon cancer;
2. hearing loss;
3. cystic fibrosis;
4. inherited susceptibility to Alzheimer's disease;
5. hereditary hemochromatosis;
6. spinocerebellar ataxias;
7. long QT syndrome; and
8. Canavan disease and Tay-Sachs disease.

The cases were chosen in part because they involve different and contrasting patenting strategies and licensing schemes. They include data from the literature and other sources regarding cost, availability, accessibility, and the quality of the tests, as well as the extent to which improvement and innovation in diagnosis, prediction, and risk assessment are facilitated. A compendium of the eight case studies can be found at Appendix 1 of this report.

In the course of its work, and to complement the case study approach, the Duke investigators recommended that a second study be commissioned involving an analysis of the licensing practice outcomes for groups of DNA patents under two different policy frameworks, one that favors nonexclusive licensing, and one that is neutral in terms of a preferred licensing approach. The study was designed to examine with particular care

licenses associated with clinical diagnostic genetic tests. It involved a comparison of licensing practice outcomes for DNA patents owned by the government and arising from NIH's intramural research program (governed by the Stevenson-Wydler Act) and those owned by not-for-profit academic research institutions (governed by the Bayh-Dole Act). Lori Pressman was hired to conduct this aspect of the SACGHS study. The study is ongoing; preliminary results are summarized in Appendix 2.

Report on Findings. The findings from the literature review, expert consultations, and case studies were compiled and analyzed. If current data were found to be lacking and conclusions could not be drawn from the findings, data gaps were described.

Part 2—Exploring International Perspectives

The United States is not alone in confronting possible conflicts related to the patenting and licensing of genetic material. Therefore, international perspectives were gathered through research and consultation to explore how other countries incentivize R&D and how they use the intellectual property system while assuring clinical and patient access to gene discoveries. SACGHS recognizes the unique patent and licensing landscape of each country including our own, but it was felt that such comparisons might illustrate lessons that hold relevance for the United States. Relevant reports were reviewed, including OECD's report on genetic licensing best practices and reports of the Australian Law Reform Commission; the Canadian Advisory Committee on Biotechnology; the Nuffield Council; the U.K. Commission on Intellectual Property Rights and Economic Development; and the Euro Patent Convention.

In addition, individuals with broad expertise in the issues at hand were consulted through a roundtable. Data gathering was focused on how intellectual property rights in gene patents or genetic tests are exercised outside of the United States, highlighting the differences between the U.S. patent system and other systems with respect to genetic information and how other countries ensure intellectual property protections and clinical/patient access.

Part 3—Gathering Public Perspectives

Public perspectives will be gathered through broad outreach mechanisms and the identification and targeting of key stakeholders (e.g., through the *Federal Register* and letters directed to specific parties). Public and stakeholder input will be compiled and summarized. Initially, the Committee thought it also would be important to hold a roundtable or hearing with key stakeholders and organizations. However, as the Task Force conducted its analysis, it became apparent that the broad public consultation process itself would capture stakeholder and organizational perspectives without limiting participation as could occur in the context of an invited roundtable or hearing.

Compilation of Preliminary Findings and Preparation of Report

The preliminary findings from the data gathering and analysis and international consultations are compiled and analyzed in the next chapter. The results of the public comment process will be compiled, considered, and integrated into the final report.

Chapter III

Preliminary Findings

As noted in the previous chapter, in an effort to determine the impact, if any, of gene patenting on patient and clinical access to diagnostic genetic tests, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) engaged in multi-faceted information gathering, including:

1) a review of the patent, licensing, and technology transfer landscape
2) a literature review
3) a review of international policies;
4) commissioning of eight case studies of clinical conditions for which genes have been patented;
5) a comparison of licensing practice outcomes for DNA patents owned by the government and arising from NIH's intramural research program (governed by the Stevenson-Wydler Act) and those owned by not-for-profit academic research institutions (governed by the Bayh-Dole Act); and
6) public comment.

The preliminary findings from all but the last of these activities are summarized in this chapter.

Overview of Patent Law and Licensing

Constitutional Basis and Rationale for the Patent System

The purpose of the U.S. patent system is to promote scientific progress. This rationale, as the Supreme Court has recognized, comes from the U.S. Constitution: "The stated

objective of the Constitution in granting the power to Congress to legislate in the area of intellectual property is to 'promote the Progress of Science and useful Arts.'" [20]

The courts generally have recognized two principal ways in which patent law promotes progress.[21] First, by "offering a right of exclusion for a limited period[,]" patents provide "an incentive to inventors to risk the often enormous costs in terms of time, research, and development [needed to create an invention]."[22] The specific right of exclusion that a patent provides is "the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States" from the time the patent issues until 20 years after the date of the patent application.[23]

The theory that patents stimulate inventive activity is based on the premise that without patents, people would not pursue inventions, because any inventions they might create could be copied by others.[24] These copiers, or "free riders," could sell the product just as easily as the original inventor, and their competition would lower the invention's price "to a point where the inventor receives no return on the original investment in research and development."[25] The right of exclusion promised by a patent in effect reassures the would-be inventor or investor that any invention that is created cannot be copied during the patent term. Reassured in this way, the would-be inventor presumably decides to pursue invention, while the would-be investor presumably becomes willing to fund such pursuits, should outside funds be needed.

In response to the above theory, some scholars have pointed out that biotechnology researchers have strong incentives to invent that are independent of patents. Academic

[20] *Kewanee Oil Co. v. Bicron*, 416 U.S. 470 (1974). This utilitarian view of patents "is distinct from moral arguments for patent protection advanced in some European countries . . . ." The drafters of the Constitution did not believe that "inventors have a natural property right in their inventions." Eisenberg, R.S. (1989). Patents and the progress of science: Exclusive rights and experimental use. *University of Chicago Law Review* 56:1017-1086, p. 1025.
[21] Eisenberg, R., op. cit.
[22] *Kewanee Oil Co. v. Bicron*, 416 U.S. 470 (1974).
[23] 35 U.S.C. § 154.
[24] Eisenberg, R., op. cit.
[25] Ibid., p. 1025.

and industry researchers, who make up the "inventor class" in genetics and biotechnology, often are motivated principally by the desire to advance understanding, develop treatments for disease, advance their career and earn the esteem of colleagues.[26] Scientists' enjoyment of research and solving complex problems also naturally leads to inventions.[27] This understanding of the motivations of scientists is consistent with the findings from the case studies discussed later in this report. Scientists interviewed as part of these case studies stated that they would have pursued their research even if their discoveries were not patent-eligible. However, from the case studies, it also appears that when researchers sought private funds to initiate or advance their genetics research, investors were willing to provide funding based on the prospect of patents being granted as a result of the research. In several cases, such research did lead to patented genetic tests. In at least one case, the investors at first had hoped that the research would lead to a patented therapeutic involving the genes.

The courts have suggested that a second way patents promote progress is through the required disclosure of the new invention.[28] In exchange for the patent right of exclusion, an inventor must publicly disclose his or her invention in a manner that enables one of ordinary skill in the inventive field to make the invention.[29] Public disclosure of an invention adds to the public storehouse of knowledge.[30] Furthermore, the disclosure of a new invention and new knowledge gives others the chance to build upon the disclosed discovery, potentially leading to further advances.[31]

[26] Golden, J.M. (2001). Biotechnology, technology policy, and patentability: Natural products and invention in the American system. *Emory Law Journal* 50:101-191. Golden acknowledges, though, that the vast majority of funding for university scientists comes from the Federal Government, which is interested in both advancing knowledge and seeing that inventions reach the public. For the latter goal, government, through the Bayh-Dole Act, encourages patenting and licensing of inventions by funded researchers.
[27] Thursby, J., and M. Thursby. (2007). Knowledge creation and diffusion of public science with intellectual property rights. *Intellectual Property Rights and Technical Change, Frontiers in Economics Series*, Vol. 2, Elsevier Ltd.
[28] Eisenberg, R., op. cit.
[29] 35 U.S.C. § 112.
[30] Eisenberg, R., op. cit.
[31] *Kewanee Oil Co. v. Bicron*, 416 U.S. 470 (1974).

The theory that patents provide an incentive to disclose is based on the premise that if inventors could not patent their inventions, they would try to maintain them as trade secrets.[32] Such secrecy is undesirable because the public is denied new knowledge.[33] The public also might waste resources duplicating the discovery.[34] The patent system, therefore, ensures that discoveries are revealed and not sequestered.

Many commentators doubt that inventors would keep their inventions secret if they could not patent them. In the area of genetics—as in nearly all science—academic researchers have strong incentives to publish and present their discoveries, because the university system encourages the norms of open science and rewards researchers who publish.[35] Scholars also point out that secrecy is not a viable option for many inventors, because their inventions could be reverse engineered.[36] However, the narrower question of whether secrecy is a viable option for biotechnology companies is unclear. No recent literature was found addressing the feasibility of maintaining genetic discoveries as secrets, particularly after a particular product was launched or a service offered. Nor was any literature found addressing the likelihood that biotechnology companies would choose secrecy if patent protection was unavailable and if trade secrecy was feasible.

Legal and economics scholars recognize a third possible mechanism by which patents could promote progress. According to this third theory, "the patent system is not so much needed to stimulate inventive activity; rather, it facilitates investment into costly and risky development processes that are necessary to transform a 'mere' invention into a marketable product."[37] Thus, this incentive would operate after a patent has been issued. Biotechnology industry representatives assert that patents, in fact, operate in this way,

[32] Eisenberg, R., op. cit.
[33] Ibid.
[34] Ibid.
[35] Fabrizio, K.R., and A. Diminin. (2008). Commercializing the laboratory: Faculty patenting and the open science environment. *Research Policy* 37:914-931; see also Bagley, M.A. (2006). Academic discourse and proprietary rights: Putting patents in their proper place. *Boston College Law Review* 47:217-274.
[36] Ibid.
[37] W.P. zu W. und P. (2008). Research tool patents after Integra v. Merck—Have they reached a safe harbor? *Michigan Telecommunications Technology Law Review* 14:367, p. 372.

helping small biotechnology companies attract the venture capital needed to further develop promising discoveries.[38]

The Government essentially endorsed this understanding of how patents operate by enacting the Bayh-Dole Act.[39] The objective of the Act is to ensure that Government-funded inventions reach the public.[40] To accomplish this goal, the Act operates to encourage academic institutions to patent and license these inventions.[41] Thus, the Government, through this Act, in effect recognizes that patents serve to stimulate the investment needed to commercially develop promising inventions.[42] It is important to note that development costs differ dramatically depending on whether such development is aimed at developing a therapy or is directed towards development of a diagnostic test.

Patentable Subject Matter

The most recent comprehensive set of patent laws were written in the Patent Act of 1952 and most recently revised by the American Inventors Protection Act of 1999. Section 101 of the 1952 Act defines the categories of patentable subject matter as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof . . . ."[43] Establishing that an invention is a machine, manufacture, process, or composition of matter is the "first door which must be opened on the difficult path to patentability . . . ."[44] After one has successfully passed through this door, an inventor must show that the invention is novel, useful, and nonobvious.[45] These criteria are discussed later in this section.[46]

[38] Ibid. See also *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy: A Report by the Federal Trade Commission*. October 2003, http://www.ftc.gov/os/2003/10/innovationrpt.pdf.
[39] Golden, J.M., op. cit.
[40] 35 U.S.C. § 200.
[41] 35 U.S.C. § 201 et seq.
[42] American Bar Association. (2002). *The Economics of Innovation: A Survey*, http://www.ftc.gov/opp/intellect/0207salabasrvy.pdf.
[43] 35 U.S.C. § 101.
[44] *State St. Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368 (Fed. Cir. 1998).
[45] Conley, J.M., and R. Makowski. (2003). Back to the future: Rethinking the product of nature doctrine as a barrier to biotechnology inventions (Part II). *Journal of the Patent &Trademark Office Society* 85:371-398.
[46] These criteria are laid out in 35 U.S.C. § 101, § 102, and § 103.

Types of Patents Associated with Genetic Tests

As noted above, patents may be obtained for four types of inventions: processes (a series of steps "to produce a given result"[47]); machines (apparatuses[48]); manufactures (defined broadly to capture useful technology[49]); and compositions of matter (synthesized chemical compounds and composite articles[50]).[51]

The patents most strongly associated with genetic testing—and the focus of this report—are composition of matter/manufacture claims to isolated nucleic acid molecules (typically for molecules that are useful as probes against genetic markers); manufacture claims to genetic test kits; process claims to diagnosis through genetic testing; and manufacture claims to gene chips and microarrays. Patented machines used for DNA sequencing or to print microarrays may be indirectly involved in genetic testing. For example, if a genetic test is performed using machine sequencing, a patented DNA sequencer might be used. Similarly, a microarray printing machine might be used to initially fashion a microarray that would be used for genetic testing. But these patents on machines do not directly protect genetic tests. The focus of this report is on those patents that can protect a genetic test, such as patents on isolated nucleic acid molecules.

Of the above four general types of patents associated with genetic testing, patents on isolated nucleic acid molecules and patents on diagnostic processes—referred to in lay terms as "diagnostic methods"—are the two most frequently associated with the genetic tests discussed in this report.[52] These two categories of patents also have generated

[47] *Cochrane v. Deener*, 94 U.S. 780 (1877).
[48] *Nestle-Le Mur Co. v. Eugene, Ltd.*, 55 F.2d 854 (6th Cir. 1932).
[49] Adelman, M.J., Rader, R.R., Thomas, J.R., and H.C. Wegner. (2003). *Cases and Materials on Patent Law, Second Edition*. Eagan, MN: Thomson West.
[50] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
[51] 35 U.S.C. § 101.
[52] A patent scholar also has observed that these two kinds of patents tend to be most relevant to genetic testing: "Practically, most clinicians operating in the shadow of genetic testing-related patents will confront composition of matter claims to the DNA gene sequences [isolated molecules] or to particular genetic mutations . . . or method claims [process claims] to the use of the nucleic acid or techniques for sequence comparison between the test sample and the reference nucleic acid. In the context of the home-brew genetic

considerable controversy. Patents on isolated nucleic acid molecules have been objected to on the basis that they seem to grant exclusive rights to something found in nature. This argument—and the legal response that these types of patents, sometimes referred to as "gene patents" or "DNA patents," are not in fact "products of nature"—is addressed below. Patents on genetic diagnostic processes or methods, which consist of a series of steps for conducting a genetic test, have been criticized for trying to patent a mere correlation. That is, these patents seem to grant exclusive rights to the correlation between a gene (or genes) and a disease. Some have argued that such biological relationships are unpatentable laws of nature or that correlations are "mental steps," not subject to protection.[53] This ongoing legal controversy also is addressed in its own subsection below.

Patents that claim a DNA molecule are the broadest types of patents associated with genetic tests. The inventor of such a nucleic acid molecule has rights to exclude all uses of the molecule.[54] A patent for a diagnostic process, on the other hand, may reference a genetic molecule—a particular gene, for example—but others could still use that gene for any purpose other than the patented process.

Legal Basis for the Patentability of Nucleic Acid Molecules

Congressional committee reports published at the time the Patent Act of 1952 was passed indicate that Congress intended patentable statutory subject matter under § 101 to "include anything under the sun that is made by man."[55]

On the other hand, things that are not made by humans—such as laws of nature, natural phenomena, and abstract ideas—are not patentable subject matter under § 101.[56] This

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tests which dominate clinical genetic testing, patent claims to diagnostic kits are less relevant." Kane, E.M. (2008). Patent-mediated standards in genetic testing. *Utah Law Review* 2008:835-874. p. 845-846.

[53] "Mental steps" is a phrase that has been used by the courts in referring to unpatentable processes based on mental operations. See, for example, *In re Comiskey*, 499 F.3d 1365 (Fed. Cir. 2007).

[54] Berman. H.M., and R.C. Dreyfuss. (2006). Reflections on the science and law of structural biology, genomics, and drug development. *UCLA Law Review* 53:1-40.

[55] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

exclusion extends to products of nature, such as minerals.[57] Based on this legal principle, the genes found in nature—the genes within a human's cells, for example—cannot be patented. However, purified, isolated DNA molecules, whether their sequence corresponds to actual genes or not, are patentable as compositions of matter or as manufactures because they do not exist in a purified, isolated form in nature.[58]

The notion that purified products of nature are patent-eligible arose out of case law in the early 1900s. In the 1911 case *Parke-Davis & Co. v. H.K. Mulford & Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911), Judge Learned Hand ruled that adrenaline purified from a gland was patentable. In finding the invention patentable, Judge Hand reasoned that purified adrenaline differed "not in degree, but in kind" from the adrenaline found in glands and was "for every practical purpose a new thing commercially and therapeutically."[59] His decision was the first to find that a purified form of a natural product merited patent protection.[60]

Since *Parke-Davis*, other courts have found inventions derived from nature to be patentable.[61] The U.S. Supreme Court considered the patentability of such inventions in the seminal case of *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). A case that was closely watched by the biotechnology community, *Diamond* concerned the patentability of a bacterium that had been genetically altered to contain plasmids capable of degrading

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[56] Ibid. No major opinion apparently has addressed whether the exclusion of laws of nature from patent-eligibility is constitutionally mandated, although this may be the case, because patents on laws of nature would not serve to promote the progress of science. For a fuller discussion of this issue, see Gibstein, R.S. (2003). The isolation and purification exception to the general unpatentability of products of nature. *Columbia Science and Technology Law Review* 4:242. Justice Breyer, in his dissent from the denial of certiorari in *Lab. Corp. v. Metabolite*, 548 U.S. 124 (2006), implies that the exclusion of laws of nature from patentability is constitutionally mandated.

[57] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

[58] The U.S. Patent and Trademark Office's (USPTO's) utility guidelines provide the conclusion that isolated, purified DNA molecules are patentable. The guidelines are available at http://www.uspto.gov/web/offices/com/sol/og/2001/week05/patutil.htm. Purification and isolation here refer not to absolute purity, but to the general absence of other large molecules and biological substances. See Chin, A. (2006). Artful prior art and the quality of DNA patents. *Alabama Law Review* 57:975.

[59] *Parke-Davis & Co. v. H.K. Mulford & Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911).

[60] Gibstein, R.S., op. cit.

[61] For example, in *Merck & Co., Inc. v Olin Mathieson Chemical Corporation*, 253 F.2d. 156 (4th Cir. 1958), vitamin B12, extracted from the liver of cattle, was found to be patentable.

oil.[62] The Supreme Court held that the bacterium qualified as a patentable manufacture or composition of matter because it was "a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility."[63] The Court continued, "[The inventor's] discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101."[64]

The *Diamond* decision signaled to the biotechnology community that genetically altered organisms could be patented. No case, however, has squarely considered the question of whether isolated nucleic acid molecules are patentable subject matter.[65] Nonetheless, the U.S. Patent and Trademark Office (USPTO), which began issuing gene patents in 1992, has cited *Parke-Davis* and *Diamond* in support of the proposition that isolated and purified DNA molecules are patentable.[66]

Some legal scholars have critiqued USPTO's conclusion for suggesting that the purification of naturally occurring substances automatically confers patentability.[67] These scholars argue that the focus of the patentability inquiry, as established in *Parke-Davis* and *Diamond*, is not on purification *per se*, but on whether an invention derived from nature differs "in some substantial and material way from the natural version."[68]

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[62] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
[63] Ibid.
[64] Ibid.
[65] Conley, J.M., and R. Makowski (Part II), op. cit.; Berman, H., and R. Dreyfuss, op. cit. In a case that came close to this question but that did not address it, the Federal Circuit considered various other challenges to a patent claiming a purified and isolated DNA molecule. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991).
[66] Conley, J.M., and R. Makowski (Part II), op. cit.; "The first patented gene was the retinoblastoma tumor suppressor gene . . . ." Koss, C. (2007). Oysters and oligonucelotides: Concerns and proposals for patenting research tools. *Cardozo Arts & Entertainment Law Journal* 25:747-773, p. 753, note 40. For USPTO's conclusion that isolated genes are patentable, see the responses to comments in the USPTO utility examination guidelines at http://www.uspto.gov/web/offices/com/sol/og/2001/week05/patutil.htm. Contrary to USPTO's conclusion, some legal commentators have argued that isolated DNA molecules do not differ "in kind," as required by *Parke-Davis*, because the information content of the isolated gene is identical to the natural form of the gene. Berman and Dreyfuss, op. cit.
[67] For such a critique, see Conley and Makowsk (Part II), op. cit.
[68] Ibid. p. 379. See also Chisum, D.S., *Chisum on Patents* (2001 & Supps.) (recognizing that in *Parke-Davis*, the focus of the patentability inquiry is on whether the pure compound differs in kind). See also Berman and Dreyfuss, op. cit. (recognizing that, to be patentable, an invention derived from nature must be different in kind from the product of nature). Conley and Makowski's statement that the invention must

Therefore, purification "is a basis for patentability only if it creates a material difference between the claimed product and its natural precursor."[69] As such, some legal scholars have called for the courts to conduct a "fact-specific inquiry into the materiality of the differences that are created by the processes such as isolation, purification, and synthesis."[70]

Whether or not courts decide to undertake this inquiry at some point in the future, for the time being, isolated and purified DNA molecules are clearly patentable.

Types of Nucleic Acid Patents

The types of purified, isolated nucleic acid molecules that have been patented as manufactures or compositions of matter include genes, single nucleotide polymorphisms, complementary DNA (cDNA), RNA, DNA probes (short stretches of DNA that may hybridize with all of a gene or just a portion of it), markers, and vectors that can be used to clone, express, or therapeutically deliver a particular genetic sequence.

The next section addresses the legal controversy regarding the patentability of diagnostic processes. Afterward, the discussion returns to patents claiming isolated nucleic acid molecules, in subsections that address the novelty, utility, and nonobviousness requirements for patentability.

Recent Case Law Relevant to Diagnostic Process Patents

Process inventions for methods of genetic diagnosis often involve a series of steps. For example, the initial steps might include—in general terms—extracting host DNA from a cell, mixing the host DNA with a genetic probe that is complementary to a genetic

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have material differences over the product of nature is simply a way of rephrasing the *Parke-Davis* requirement that the invention differ in kind from the product of nature.

[69] Conley, J.M., and R. Makowski (Part II), op. cit.

[70] Ibid. The authors state that under this test, one could make reasonable arguments both for and against the patent-eligibility of purified DNA molecules.

disease marker, and determining whether the probe hybridized to the marker. The last step would be to interpret the results of this procedure. Where a probe signal was present (because the probe had hybridized to the marker), this might mean that the patient had a specific disease-associated mutation. Conversely, lack of a signal would indicate absence of that mutation.

Critics of the patenting of such "diagnostic processes" or "diagnostic methods" argue that these processes should not be patent-eligible because they involve unpatentable fundamental laws of nature—namely, the relationship or association between a particular genetic sequence and a disease. Whether the courts will agree with this viewpoint is unclear at the moment. In a recent case, *In re Bilski*, No. 2007-1130, slip op. (Fed. Cir. Oct. 30, 2008), the Federal Circuit Court of Appeals defined the test that governs whether a process qualifies as patent-eligible subject matter under 35 U.S.C. § 101 or is unpatentable as a law of nature. Citing U.S. Supreme Court precedent, the court first recognized that processes that involve a specific application of an abstract idea or natural law are patent-eligible, even though abstract ideas and natural laws themselves are not patentable. The court then elaborated that a process is limited to a specific application of an abstract idea or natural law (and thus patentable) if (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing.

The patented process in question in *Bilski* was not a diagnostic method, but "a method of hedging risk in the field of commodities trading."[71] Nonetheless, the court's test now will be applied to genetic diagnostic processes to determine their patentability. Whether a typical genetic test would pass this test is an open question. The answer will depend on how patent examiners and courts interpret the precise meaning of "machine" and "transformation." The *Bilski* court indicated that future decisions will refine "the precise

[71] *In re Bilski*, No. 2007-1130, slip op. (Fed. Cir. Oct. 30, 2008).

contours" of what qualifies as a machine or apparatus.[72] Patent law observers also believe that guidance from the courts is needed on what qualifies as a transformation.[73] Although the majority opinion in *Bilski* did not reference diagnostic tests, Judge Rader filed a separate opinion in which he commented on the patentability of diagnostic processes.[74] First, though, Judge Rader rejected the court's "machine or transformation" test.[75] He argued that the court's test imposes conditions on the patentability of processes that have no basis in the Patent Act.[76] He elaborated, "[T]he only limits on eligibility [for patents] are inventions that embrace natural laws, natural phenomena, and abstract ideas."[77] Rader then went on to explain that although biological relationships cannot be patented because they are natural laws, diagnostic processes that employ these relationships for a specific useful end can be.[78]

Therefore, under Judge Rader's understanding of the patent statute, a process for diagnosing a disease based on the biological relationship between a gene and a disease would be patentable. Of course, his views, filed as they were in a separate opinion, do not establish legal precedent. And so, for the moment, no court decision has directly answered whether diagnostic processes qualify as patentable subject matter or are unpatentable laws of nature.

Should the *Bilski* decision be appealed, the U.S. Supreme Court will have the chance to answer this question. The prospects for the Supreme Court taking up the case are unclear. The Court in 2006 ultimately passed on deciding a similar case, *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 370 F.3d 1354 (2004).[79]

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[72] Ibid.
[73] *Patentable Subject Matter: In re Bilski*, Edwards Angell Palmer & Dodge Client Advisory, December 2008, http://www.eapdlaw.com/files/News/890e09d5-1e31-4e54-808a-11a8921b20e2/Presentation/NewsAttachment/5099ba4c-ebe0-4e79-b87b-120455063ed1/2008-CA-Bilski.pdf.
[74] *In re Bilski*, No. 2007-1130, slip op. (Fed. Cir. Oct. 30, 2008).
[75] Ibid.
[76] Ibid.
[77] Ibid.
[78] Ibid.
[79] *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006). The Court granted the writ of certiorari, heard oral arguments, and then dismissed the writ of certiorari as improvidently granted.

Lab. Corp. concerned the patentability of a diagnostic process consisting of assaying a body fluid for homocysteine and then correlating an elevated level of homocysteine with a vitamin B deficiency.[80] The university doctors who patented the process had discovered the biological relationship between these two substances.[81] When the case was before the Federal Circuit Court of Appeals, the Federal Circuit did not reach the issue of the patentability of the process, deciding the case on other grounds.[82] The case was appealed to the U.S. Supreme Court, which dismissed it after initially granting certiorari and hearing oral arguments.[83] Justice Breyer, joined by Justice Stevens and Justice Souter, dissented from the dismissal, arguing that the diagnostic process in *Lab. Corp.* was nothing more than an unpatentable natural phenomenon.[84] (Rader's separate opinion in *Bilski* was in part a rebuttal to Breyer's viewpoint.)

So far, the opinions by Rader and Breyer are the only opinions that comment on the patentability of diagnostic processes, and neither opinion is precedential. Potential court guidance on this issue is on its way, however. An upcoming Federal Circuit decision, *Prometheus v. Mayo*, concerns the patentability of life science processes.[85] This case may provide guidance on how to apply the "machine or transformation" test of patentability in a life sciences context. That guidance, in turn, may be applicable to genetic diagnostic processes particularly. However, the larger question—and one that must await U.S. Supreme Court guidance—is whether the "machine or transformation" test is appropriate at all.

[80] Ibid.
[81] Ibid.
[82] Ibid.
[83] Ibid.
[84] Ibid.
[85] B. Fiacco, *In re Bilski: Trouble Ahead for Biotech?* Foley Hoag LLP Intellectual Property Alert, November 6, 2008, http://www.foleyhoag.com/newscenter/publications/alerts/intellectual-property/intellectual-property-alert_110608.aspx?ref=1. In a related case, *Classen Immunotherapies, Inc. v. Biogen IDEC*, the Federal Circuit held in a nonprecedential opinion that a process for evaluating vaccine schedules was unpatentable under § 101 because it did not involve a machine or transformation. *Federal Circuit Invalidates Immunization Patent for Lack of Patentable Subject Matter*, Patent Law Blog, http://www.patentlyo.com/patent/2008/12/federal-circu-2.html.

The Novelty, Utility, and Nonobviousness of Patents Claiming Isolated Nucleic Acid Molecules

As stated earlier, once a patent applicant has established that the invention he or she claims is patentable subject matter under § 101, the claimed invention then must be found to be novel, useful, and nonobvious for a patent to issue. The sections below discuss some of the relevant considerations in this area for patents claiming nucleic acid molecules. Relevant USPTO actions and case law decisions also are discussed.

Novelty

Determining whether a particular invention is novel or new can be a complicated inquiry in patent law. One circumstance in which an invention will be found to lack novelty is where a printed publication or patent pre-dates the claimed invention and describes every aspect of it.[86]

Relying in part on this rule, pharmaceutical companies such as Merck and organizations such as the Wellcome Trust have initiated efforts to publish, without patenting, DNA molecules.[87] Merck, for example, in 1994 "announced that it would sponsor a human cDNA sequencing project at the Washington University School of Medicine in St. Louis wherein the results would be published immediately in the 'Merck Gene Index,' a public domain database."[88] Merck's and others' hope was that these published sequences would defeat on novelty grounds later claims to the same molecules.[89] These companies and organizations are trying to limit the number of DNA patents because they are concerned that these patents may limit their efforts to conduct disease research.[90]

Utility

[86] *Paeco, Inc. v. Applied Moldings, Inc.*, 562 F.2d 870 (3d Cir. 1977).
[87] Chin, A. (2006). Artful prior art and the quality of DNA patents. *Alabama Law Review* 57:975-1039.
[88] Ibid. p. 1016.
[89] Chin, A., op. cit. Chin indicates that these efforts in fact have not defeated many patent claims; the reasons for this do not appear to be explained in the article.
[90] Ibid.

An invention must be useful in order to be patentable. The standard of utility in patent law is particularly important in biotechnology. In January 2001, USPTO published in the *Federal Register* "Utility Examination Guidelines" that explain the procedure patent examiners use in judging utility.[91] Although these guidelines, which have so far met with approval by the Federal Circuit,[92] govern utility determinations for all patent applications, they were promulgated specifically to address concerns about the patentability of expressed sequence tags and cDNA.[93] The utility guidelines require that inventions have a specific, substantial, and credible utility.[94] In the case of a patent claiming a DNA molecule useful as a probe, the proffered utility would be specific if it stated the particular gene with which the probe would be hybridized; the utility would be substantial if it involved a "real world" use, such as diagnosis of disease; and the utility would be credible if the probe could in fact be used for that purpose.[95] A patent applicant's assertion that a DNA molecule is useful as a probe is considered by the USPTO to be *per se* credible.[96]

The higher standard of utility established with these guidelines was meant to prevent applicants from seeking patents on nucleic acid molecules, particularly on molecules with only partial gene sequences for which they had not yet identified a genetic function. According to then USPTO Director Q. Todd Dickinson, "One simply cannot patent a gene itself without also clearly disclosing a use to which that gene can be put."[97]

Nonobviousness

[91] Utility Examination Guidelines, http://www.uspto.gov/web/offices/com/sol/notices/utilexmguide.pdf.
[92] *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005).
[93] Thomas, J.R. (2000). *An Examination of the Issues Surrounding Biotechnology Patenting and its Effect Upon Entrepreneurial Companies*. Congressional Research Service Report (August 31, 2000).
[94] Ibid.
[95] Ibid.
[96] Ibid.
[97] Dickinson, Q.T. (2000). Statement, House Judiciary Committee, Subcommittee on Courts and Intellectual Property (July 13 2000), http://www.uspto.gov/web/offices/ac/ahrpa/opa/bulletin/genomicpat.pdf.

An invention cannot be patented if it would have been obvious to one of ordinary skill in the particular inventive field.[98] Patents were not designed to protect marginal improvements to technology that are obvious and to be expected.[99] For an invention to be patentable, then, it must be nonobvious. What type of advance qualifies as nonobvious? A full answer to that question is beyond the scope of this report. Essentially, though, in judging nonobviousness, one compares the prior art—the prior knowledge and technology in a particular field—to the claimed invention and then judges whether the invention represents a sufficient advance over the prior knowledge.[100]

With respect to patents claiming DNA molecules, the United States' test for nonobviousness has changed since two seminal cases in the mid-1990s, *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) and *In re Deuel*, 51 F.3d. 1552 (Fed. Cir. 1995). In *Bell*, which is substantially similar to *Deuel*, the Federal Circuit considered an appeal from USPTO's rejection, on obviousness grounds, of patent applications claiming DNA molecules. The particular DNA molecules in question corresponded to insulin-like growth factor (IGF) proteins.[101] The prior art that the USPTO examiner had reviewed to make the obviousness determination consisted of two important pieces: the amino acid sequence of IGF proteins and a published laboratory procedure.[102] That laboratory procedure provided instructions for taking a protein sequence, creating a DNA probe from it using the genetic code, and then using that probe to obtain the protein's gene.[103] The patent applicants in *Bell* had used the known IGF amino acid sequence, created a DNA probe from it, and then used the probe to obtain the IGF gene.[104] As a final step, the patent applicants sequenced this gene, with that sequenced molecule claimed as an invention.[105] USPTO believed that based on the prior art, it would have been obvious to an ordinary

[98] 35 U.S.C. § 103.
[99] Adelman, et al., op. cit.
[100] *Graham v. John Deere Co.*, 383 U.S. 1 (1966).
[101] *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993).
[102] Ibid.
[103] Ibid.
[104] Ibid.
[105] Ibid.

molecular biologist to "find the nucleic acid when the amino acid sequence is known . . . ."[106]

The Federal Circuit Court of Appeals disagreed, holding the invention was nonobvious.[107] The court acknowledged that "one can use the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining that gene."[108] Nonetheless, because the genetic code is degenerate, with most amino acids corresponding to at least two different possible nucleotide sequences, the actual sequence of the gene could never be predicted.[109] In essence, the court found that the inability of one to predict on paper the gene's sequence made the resulting molecule, sequenced by a machine, nonobvious.

Legal commentators have critiqued the court's analysis, arguing that the focus of the inquiry should be on whether the laboratory procedures to obtain the gene would be obvious—not whether one could know beforehand, on paper, the gene's exact sequence.[110] However, this viewpoint was directly rejected by the Federal Circuit in *Deuel*. There, the Federal Circuit noted that even though it might have been "obvious to try" a standard method to obtain a gene from a protein, "'obvious to try' has long been held not to constitute obviousness."[111]

However, in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007), the U.S. Supreme Court recently signaled a different viewpoint, noting "the fact that a combination was obvious to try might show that it was obvious."[112] Although *KSR* did not involve a biotechnology invention, the Board of Patent Appeals and Interferences

[106] Ibid.
[107] Ibid.
[108] Ibid.
[109] Ibid.
[110] Cannon, B.C. (1994). Toward a clear standard of obviousness for biotechnology patents. *Cornell Law Review* 79:735-765; see also Rai, A.K. (1999). Intellectual property rights in biotechnology: Addressing new technology. *Wake Forest Law Review* 34:827-847.
[111] *In re Deuel*, 51 F.3d. 1552 (Fed. Cir. 1995).
[112] The Supreme Court's principal holding in *KSR*, which did not involve a biotechnology invention, was to reaffirm the test of nonobviousness first laid out by the Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966).

recently relied on it in deciding a case with facts similar to *Deuel*. In *Ex parte Kubin*, the Board rejected as obvious a DNA molecule whose sequence was derived from a known protein.[113] The Board reasoned that for an ordinary molecular biologist with a protein in hand, it would be obvious to isolate and sequence the corresponding DNA.[114] In other words, such sequencing would be "obvious to try." Although the Board asserted that *Deuel* was not relevant to the case, insofar as *Deuel* might be considered relevant, the Board found that the *KSR* decision overruled the *Deuel* principle that obvious to try does not constitute obviousness.[115]

Patent law scholars and observers appear divided over whether *Kubin* correctly interpreted *KSR*. Although some believe *KSR* supports the *Kubin* view, others argue that *KSR* did not abrogate *Deuel's* central holding: namely that "the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious . . . ."[116] *Kubin* has been appealed to the Federal Circuit Court of Appeals, which will have the chance to say if it understood *KSR* to overrule its principal holding in *Deuel*. Ultimately, though, only the U.S. Supreme Court has the ability to definitively answer this question. In the meantime, USPTO has enacted "Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex, Inc.*"[117] These guidelines cite the *Kubin* decision as an example of how to apply the "obvious to try" rationale for supporting a finding of obviousness.[118]

[113] *Ex Parte Kubin & Goodwin*, No. 2007-0819, 2007 WL 2070495 (Bd.Pat.App. & Interf. May 31, 2007).
[114] Ibid.
[115] Ibid.
[116] *In re Deuel*, 51 F.3d. 1552 (Fed. Cir. 1995). For support of the *Kubin* decision as "well-founded under *KSR*," see Eisenberg, R. (2008). Pharma's nonobvious problem. *Lewis & Clark Law Review* 12:375-430; for criticism of the Board's reasoning in *Kubin*, see K.E. Noonan, *Ex parte Kubin (B.P.A.I 2007)*, Patent Docs, July 18, 2007, http://patentdocs.typepad.com/patent_docs/2007/07/ex-parte-kubin-.html.
[117] Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex, Inc.*, Effective October 10, 2007, http://www.uspto.gov/web/offices/com/sol/og/2007/week45/patgide.htm.
[118] Ibid.

These guidelines signal that the patent office will consider obvious and unpatentable any applications that claim a DNA molecule derived from a known protein.[119] But even DNA molecules derived through other means may be unpatentable after *KSR* and *Kubin*.[120] As one patent law observer noted, "As a practical matter, if obviousness of a gene hinges on whether there was a known technique that could have been used to clone the gene, few if any gene inventions will pass muster."[121] Therefore, unless *Kubin* is reversed, researchers may no longer be able to obtain patents on nucleic acid molecules. Issued patents on nucleic acids may also be invalidated. Those interested in invalidating issued patents can challenge a patent's validity through a reexamination procedure, through a declaratory judgment action, or through a counterclaim while defending against an infringement lawsuit.[122]

The Number of Human Genes Referenced in Patent Claims

By one estimate, 20 percent of the genes identified so far in the human genome are referenced in the claims of patents.[123] This corresponds to 4,382 genes of the 23,688 genes in a database, as of 2007.[124] Jensen and Murray determined these numbers by first searching for all patents that include nucleotides sequences in the claims (the claims section of a patent describes what is precisely claimed as the invention) and correlating

[119] Ibid.
[120] Eisenberg argues that *KSR* represents not a new nonobviousness doctrine but an admonishment of the Federal Circuit for failing to follow long-established principles for judging nonobviousness with regard to patents claiming nucleic acid molecules. If the Federal Circuit had followed these principles, *Bell* and *Deuel* would have been decided differently. Eisenberg, R., op. cit.
[121] Fraser, J.K. (2008). U.S. gene patents in legal limbo—for now. *Genetic Engineering and Biotechnology News*, April 1, http://www.genengnews.com/articles/chitem.aspx?aid=2422.
[122] The reexamination procedure can be found in Chapter 30 of United States Code Title 35. Some legal commentators have learned that the USPTO is working on establishing standards for determining when a reexamination challenge to an issued patent claiming a nucleic acid molecule raises "a substantial new question of patentability," as required by 35 U.S.C. § 303(a). It seems that challengers will not be able to merely cite *KSR* and ask for a re-review of the cited prior art. Stern, R.G., Bass, K.C., Wright, J.E., and M.J. Dowd. (2007). *Living in a Post-KSR World*, working paper created for The Sedona Conference on Patent Litigation VIII, http://64.237.99.107/media/pnc/1/media.121.pdf. The declaratory judgment action is made under 28 U.S.C. 2201.
[123] Jensen, K., and F. Murray. (2005). Intellectual property landscape of the human genome. *Science* 310:239-240.
[124] Ibid.

the sequences with mRNAs from the human genome.[125] The genes referenced in the claims are distributed over 4,270 patents "owned by 1156 different assignees (with no adjustments for mergers and acquisition activity, subsidiaries, or spelling variations)."[126] Of these patents, 63 percent are assigned to private firms.[127] It is important to note, however, that even when a patent claim contains a nucleotide sequence, it does not necessarily mean that the isolated nucleic acid molecule that corresponds to that sequence is the actual patented invention. In some cases, the patent may be claiming the isolated molecule as the invention, but in other cases, the patent could be claiming something entirely different.

According to the Jensen and Murray findings, some genes are referenced by multiple patent claims, with each patent describing a different type of invention, such as a cell line or a diagnostic process.[128] Such multiple claims referencing a particular gene can arise in either of two ways. First, in the case where a patent mentions a nucleic acid molecule but does not claim it as the invention itself (as in the case of a diagnostic process), other inventions involving the molecule could be patented. Second, even when the isolated molecule itself is patented, any undisclosed uses for that molecule may subsequently be patented as processes; however, any new use patent issued would require a license from the original patentee.[129]

The finding that approximately 20 percent of human genes are referenced in patent claims could have significant implications for the development of multigene (multiplex) genetic tests and the anticipated eventual development of whole-genome sequencing for clinical use.[130] Furthermore, ownership of these patents is spread over a large number of

[125] Ibid. The researchers specifically conducted a search of the patent database looking for the phrase "SEQ ID NO" in the claims. This phrase stands in for the particular nucleotide sequence that is disclosed later in the patent.
[126] Ibid., p. 239.
[127] Jensen, K., and F. Murray, op. cit.
[128] Ibid.
[129] Merges, R.P., and R.R. Nelson. (1990). On the complex economics of patent scope. *Columbia Law Review* 90:839-916
[130] As explained earlier, it is not clear how many of these genes are actually claimed as the invention. Nor is it clear how many of the patents reference the gene in claiming a diagnostic process relying on that gene.

assignees. With so many genes referenced in patents held by numerous assignees, it may be difficult for any one developer to obtain all the needed licenses to develop multiplex tests and whole-genome sequencing.

Another study that looked at how many patents contain a nucleic acid-specific term in at least one claim found that 78 percent of the discovered patents were owned by for-profit entities.[131] However, as with the Jensen and Murray study, even if the claims section of a patent contains a nucleic acid-specific term, the patent may be claiming, as the invention, something other than the isolated nucleic acid molecule. This study also found that 15 percent of such patents were for inventions that arose from federally funded research.[132]

These studies do not specifically address the number of patents associated with genetic tests, and it is not clear whether the findings can be extrapolated to infer the distribution of such patents among government, non-profits, and private entities. Nor is it clear whether these results can be extrapolated to infer the percentage of such patents that arose from federally-funded research. One researcher involved with the second study suggests that such information is not known.[133]

Infringement Exemption Does Not Extend to Biotechnology Inventions

In 1996, U.S. patent law was amended[134] to exempt medical practitioners from infringement liability for using patented medical or surgical techniques in medical practice. Under the revised law, a court could decide that a physician had infringed a patent but could not order that physician to pay damages or to stop using the technique.

These two types of patent claims—a claim to the molecule and a claim to a diagnostic process—are the ones that most often protect existing genetic tests.

[131] Pressman L., et al. (2006). The licensing of DNA patents by US academic institutions: an empirical survey. *Nature Biotechnology* 24:31-39.

[132] Ibid.

[133] Cook-Deegan, R. personal communication.

[134] 35 U.S.C. § 287(c). This is sometimes referred to as the Frist-Ganske medical procedures exemption statute.

However, clinicians and clinical laboratories, under the provision, are not exempt from liability when they infringe biotechnology patents, such as those protecting genetic tests. In 2002, Representative Lynn Rivers (D-MI) introduced the Genomic Research and Diagnostic Accessibility Act of 2002, which would have allowed researchers and medical practitioners to use patented genes sequences for noncommercial research purposes and would have exempted clinicians using genetic tests from patent infringement liability.[135] The bill did not become law.[136]

The statutory experimental use exemption from patent infringement liability, found in the Hatch-Waxman Act, may apply to research for the purpose of developing genetic test kits and reagents for genetic testing, as well as any clinical testing conducted as part of that research.[137] The Supreme Court indicated that this exemption "extends to all use of patented inventions that are reasonably related to the development and submission of *any* information under the FDCA [Food, Drug, and Cosmetic Act]."[138] However, this exemption would not extend to clinical genetic testing services.[139] Nor could it be used for research designed to develop a CLIA-approved genetic testing service; most genetic testing is done through these laboratory-developed tests rather than through test kits sold as medical devices.[140] In addition, even if the exemption protects research to develop a genetic test kit, if the test kit that is ultimately developed relies on a patented gene or diagnostic process, marketing of that kit would necessarily infringe the patent.

Freedom to Operate

Companies wishing to offer a particular genetic testing service or to sell a genetic testing kit may solicit a formal opinion on their "freedom to operate"—that is, their ability to offer the service or kit without infringing existing patents held by others. When a

[135] NIH Office of Legislative Policy and Analysis, http://olpa.od.nih.gov/legislation/107/pendinglegislation/9gene.asp.
[136] See http://www.govtrack.us/congress/bill.xpd?bill=h107-3967.
[137] Kane, E.M., op. cit.; 35 U.S.C. § 207(e)(1).
[138] *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005) (emphasis in original).
[139] Kane, E.M., op. cit.
[140] Ibid.

company does not have freedom to operate because of patents held by others, the company has several options if it wishes to proceed without infringement: the company can seek a license to practice the existing patent(s), the company can modify its product or service so that it does not infringe (this is often referred to as "designing around" a patent), or the company can seek to purchase the patent(s) at issue. Patents can be purchased, just as real property can be bought. Licensing, on the other hand, is akin to leasing or renting. Companies may also choose to market a testing service or kit without first determining their freedom to operate.

Licensing

Patent law does not address licensing practices, and USPTO does not regulate licensing practices.

A patent does not allow or compel a patent owner to take any action whatsoever including using the technology themselves. Rather, it grants the patent holder the right to exclude others from making, using, selling, offering for sale, or importing the invention, for a term of 20 years from the date of filing a patent application. A license is the usual legal instrument and technology transfer tool that a patent owner may use to grant to another person/entity the right to use the patented invention. Licenses may be exclusive or nonexclusive and may include any number of terms and conditions (e.g., financial arrangements for or restrictions on its use and due diligence requirements that require the development of the invention into a product or service).

A patent holder's options include 1) completely restricting use by anyone and not developing the technology themselves; 2) creating a monopoly situation in which the patent holder is the only user; 3) providing an exclusive license to a single user or co-exclusive licenses to a limited number of users that have agreed to develop the patented technology into a product(s) or service(s); 4) licensing the patented technology exclusively in each narrow field of use (as discussed further below); 5) granting broad nonexclusive licensing of the patented technology, and 6) making a patented technology

publicly available without asserting any rights, which allows anyone to use the patented invention for any purpose (but no user has agreed or committed to develop the patented technology into a future product or service that would become available for consumer use).

Field of use licenses can be exclusive for a particular use but permit others to develop other applications in different fields of the patented invention. Under this strategy, the licensor can grant exclusive rights to different licensees in distinct markets or application areas. Alternatively, the licensor could grant one exclusive field-of-use license and grant nonexclusive licenses to the remaining fields. Often, a licensor will attach diligence conditions to the exclusive license that require technology development.

Those holding patents protecting genetic tests may rely on both nonexclusive and exclusive licenses. When a genetic test would be applicable to different diseases or could be used in multiple contexts (newborn screening and carrier screening), field of use licenses, either exclusive or nonexclusive, may be used. In the therapeutics area, companies prefer exclusive licenses for different components of a disease.

Consideration for being granted an exclusive or a nonexclusive license can be through royalties based on sales of a product or service, increased research funding, access to state-of-the art equipment or related technologies, collaborations to develop patented technologies jointly and leverage one another's expertise, cross-licenses, stock grants, and/or annual licensing fees. Other considerations can be made through the achievement of milestones, up-front payments, or a combination of both. Consideration or payment types can depend on the stage of development of the product. A patent holder who licenses a small company tends to require fewer up-front payments but more royalties and/or a transfer of stock ownership. Determining royalty amounts and other considerations can be complicated and depends on the stage of development, the type of technology, the strength of the protection of the intellectual property, the size of the market for the gene and disease (i.e., its incidence and prevalence), the time necessary for clinical and/or public acceptance of a new product or service; the size and resources of

the licensee available for product and service development, market segment royalty ranges, and the negotiators.

Insights into the relative merits of non-exclusive versus exclusive licensing are available in a 2006 report from the U.S. Department of Agriculture's (USDA's) Economic Research Service. The report, "Government Patenting and Technology Transfer," describes case studies of patenting and licensing of government-owned inventions by the USDA's Agricultural Research Service (ARS).[141] Before turning to the findings, the USDA report presents an overview of the kinds of considerations that inform licensing decisions by technology transfer offices. Companies will only take a license if they can achieve a return on their considerable investments to develop an invention.[142] As a result, technology transfer offices try to craft license terms that make the developer willing to take investment risks.[143] One approach to enticing potential developers involves offering exclusive licenses, as these licenses ensure that the developer will not have to compete against other developers of the invention.[144] And in fact, the USDA report found that potential licensees expressed a preference for exclusive licenses because they eliminate the risk of competition from other licensees.[145] The report also found that in some cases inappropriately broad licensing may have reduced incentives for further product development.[146] The report observed, however, that "under the right market conditions and licensing strategies, multiple co-exclusive license agreements did not pose a barrier to successful technology transfer in some case studies."[147] And, moreover, multiple licenses can maximize the public use of an invention.[148] The report notes, "[i]n general, suppliers in competitive markets offer lower prices and thus encourage more widespread

[141] Heisey, P.W., J.L. King, K.D. Rubenstein, and R. Shoemaker. (2006). "Government Patenting and Technology Transfer." USDA Economic Research Report No. (ERR-15), available at http://www.ers.usda.gov/publications/err15/ [accessed February 11, 2009]. The report includes a chart presenting the various degrees of exclusivity that can exist in licenses.
[142] Ibid.
[143] Ibid.
[144] Ibid.
[145] Ibid.
[146] Ibid.
[147] Ibid. P. 35. The report defines co-exclusive licenses as ones that may be in overlapping fields or territories. On the spectrum of exclusivity, these kinds of licenses are toward the non-exclusive end.
[148] Heisey, P.W., op. cit.

introduction of the technology adoption. Co-exclusive licenses and other less exclusive licensing agreements increase competitive pressure compared with sole exclusive licenses."[149]

Since multiple licenses can sometimes accelerate technology introduction and other times limit it (by reducing development incentives), when are they most appropriate? The USDA report concludes that "[l]icensing to more than one firm is more likely to be successful if the market is segmented geographically or by stages in a production process than if all firms are competing for the same market niche."[150]

Geographic segmentation of a market, however, is just one of several factors that must be considered in choosing a licensing strategy:

> Licensee business plans, market size, profitability, and the availability of substitutes for the invention are some of the relevant factors that determine the degree of exclusivity that potential licensees will accept. For instance, one business plan might involve selling a product or service based on the invention at a small profit margin, but to a large number of customers. In a potentially profitable market where one licensee would have trouble satisfying demand for the product, it appears that additional supply from competitors under co-exclusive licenses did not slow down licensee development efforts. . . . However, if competition with other licensees [would erode] the already small profit margin, licensees may balk at taking out a license and technology transfer may not occur.[151]

The USDA report acknowledges that while these factors can in theory guide licensing decisions, in reality patent holders and prospective licensees have difficulty assessing the particular market conditions their technology will face.[152] As a result, "[f]lexible licensing approaches, including renegotiation, may be necessary as more is learned about a technology and the market in which the technology is commercialized. Against this

[149] Ibid. P. 35-36.
[150] Heisey, P.W., op. cit. P. 46.
[151] Heisey, P.W., op. cit. P. 36.
[152] Heisey, P.W., op. cit.

flexible approach, technology transfer officers must weigh the need for credible commitments from both sides."[153]

Technology Transfer Practices and Policies

The Federal Government supports a significant amount of biomedical research. Prior to 1980, there was no Government-wide policy for inventions made by the Government's grantees and contractors. The Government retained ownership of most inventions created with Federal funding, and very few of these were developed successfully into useful products or services. In 1980, the Federal Government held title to more than 28,000 patents, and fewer than 5 percent of these were licensed to industry for commercial development.[154]

The Patent and Trademark Amendments of 1980 (P.L. 96-517, also known as the Bayh-Dole Act, after its authors) was signed into law in December of 1980 and became effective July 1, 1981. It was enacted to increase U.S. competitiveness and economic growth by promoting the transfer of inventions made with Government funding by Government grantees and contractors to the private sector for development into commercial products and services that would be beneficial and become available to the public. The Bayh-Dole Act allows Federal contractors and grantees to elect title to and patent their inventions that are conceived or first actually reduced to practice in the performance of a Federal grant, contract, or cooperative agreement. The Act's policy and objective is "to promote the utilization of inventions arising from federally supported research or development . . . [and to promote] collaboration between commercial concerns and nonprofit organizations . . . ."[155] With respect to any invention in which the contractor or grantee elects rights to an invention, the Federal Government is granted a "nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced

[153] Heisey, P.W., op. cit. P. 38
[154] U.S. Government Accounting Office (GAO) Report to Congressional Committees. (1998). *Technology Transfer, Administration of the Bayh-Dole Act by Research Universities*. May 7.
[155] 35 U.S.C. § 200.

for or on behalf of the United States any subject invention throughout the world . . . ."[156] On November 1, 2000, the Bayh-Dole Act was amended to ensure that inventions made under it were used "without unduly encumbering future research and discovery."[157] Regulatory provisions associated with the enactment of the Bayh-Dole Act of 1980 stipulated the need for all grantees or contractors to report on activities involving the disposition of certain intellectual property rights that result from federally funded research (37 C.F.R. Part 401).

To facilitate compliance with these legal requirements, the Interagency Edison (iEdison) tracking system and database was designed, developed, and implemented in 1995. This system facilitates and enables grantee and contractor organizations to directly input invention data as one means of fulfilling the reporting requirement. Since 1997, iEdison participation has grown to more than 1,300 registered grantee or contractor organizations supported by any of more than 27 Federal agency offices. Use of iEdison, however, is voluntary for inventions and patents developed under Federal funding agreements.

On October 21, 1980, two months before the Bayh-Dole Act was passed, the Stevenson-Wydler Technology Transfer Act of 1980 was passed by Congress, and in 1986, the Federal Technology Transfer Act (FTTA) of 1986 amended the Stevenson-Wydler Act. Similar to the purpose of the Bayh-Dole Act, FTTA's purpose is "[t]o promote United States technological innovation for the achievement of national economic, environmental, and social goals, and for other purposes."[158] FTTA authorizes Federal agencies to transfer federally owned technology to the private sector for product development and authorizes the use of cooperative research and development agreements between Federal laboratories and nonfederal entities. Although there are similarities between the Bayh-Dole Act and FTTA, the latter has several distinct features, including the following: 1) a license may be granted only if the applicant has supplied a satisfactory plan for development and/or marketing of the invention[159]; 2) notices are published in the *Federal Register* of exclusive or partially exclusive licenses for federally owned

[156] 35 U.S.C. § 202(c)(4).
[157] 35 U.S.C. § 200.
[158] 15 U.S.C. § 3701.
[159] 37 C.F.R. 404.5(a)(1).

inventions that include the prospective licensee's name and a period of time for objection[160]; and 3) the grant of a license will not tend to substantially lessen competition.[161] The FTTA also limits the term and scope of exclusivity to not greater than reasonably necessary to provide the incentive for bringing the invention to practical application or otherwise promoting the invention's utilization by the public.[162]

NIH's Technology Transfer and Data Sharing Policies

NIH's intramural patent policy has been developed to be consistent with the Stevenson-Wydler Act and its amendments. The policy, applying to inventions developed in its intramural research programs, provides for the use of patents and other technology transfer mechanisms (such as license agreements, material transfer agreements, and research only licenses) for biomedical technologies only when a patent facilitates the availability of the technology to the public for preventive, diagnostic, therapeutic, research, or other commercial uses. When commercialization and technology transfer can best be accomplished for intramural-made inventions without patent protection, such protection typically is not sought. NIH licensing policy for intramural-developed technologies seeks to promote the development of each technology for the broadest possible application and requires that commercial partners expeditiously develop the licensed technology. NIH only uses partially exclusive or exclusive licensing for its intramural-developed inventions when it is a reasonable and necessary incentive for the licensee to risk capital and resource expenditures to bring the invention to practical application or otherwise promote the invention's utilization.[163] If it is determined by NIH that a grant of an exclusive or partially exclusive license is necessary for further development of the technology, the terms and conditions of such exclusivity are narrowly tailored and are not greater than reasonably necessary.[164]

[160] 37 C.F.R. 404.7(a)(1)(i).
[161] 37 C.F.R. 404.7(b)(1)(iii).
[162] 37 C.F.R. 404.7(C).
[163] 37 C.F.R. 404.7 (a)(1)(ii)(B).
[164] 37 C.F.R. 404.7(a)(1)(ii)(C).

In addition, NIH policy on research tools encourages sharing of tools developed by NIH-funded grant recipients. The *NIH Principles and Guidelines on Sharing Biomedical Research Resources* [165] state that the goal of public benefit should guide those who are receiving NIH funds. NIH may enact some restrictions with regard to the ownership and licensing of inventions under certain NIH-funded programs. For example, NIH has, for certain NIH-funded programs, required grantees to comply with the 2005 guidance document, *NIH Best Practices for the Licensing of Genomic Inventions*, [166] as a term of a grant or contract award. In cases for which the best practices are not a grant term, NIH still encourages grantees and contractors to comply with the practices (see Box A for the best practices). In order to meet some NIH programmatic and research goals, NIH has also determined that certain research findings, such as those involving full-length cDNA sequences from humans, rats, and mice, must be made available to the research community in named databases.

Box A: NIH Best Practices for the Licensing of Genomic Inventions

The optimal strategy to transfer and commercialize many genomic inventions is not always apparent at early stages of technology development. As an initial step in these instances, it may be prudent to protect the intellectual property rights to the invention. As definitive commercial pathways unfold, those embodiments of an invention requiring exclusive licensing as an incentive for commercial development of products or services can be distinguished from those that would best be disseminated nonexclusively in the marketplace.

Whenever possible, nonexclusive licensing should be pursued as a best practice. A nonexclusive licensing approach favors and facilitates making broad enabling technologies and research uses of inventions widely available and accessible to the scientific community. When a genomic invention represents a component part or background to a commercial development, nonexclusive freedom-to-operate licensing may provide an appropriate and sufficient complement to existing exclusive intellectual property rights.

[165] HHS. (1999). NIH Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice. *Federal Register* 64(246). December 23. Notices. P. 72090, http://ott.od.nih.gov/pdfs/64FR72090.pdf.
[166] See http://ott.od.nih.gov/policy/genomic_invention.html.

In those cases where exclusive licensing is necessary to encourage research and development by private partners, best practices dictate that exclusive licenses should be appropriately tailored to ensure expeditious development of as many aspects of the technology as possible. Specific indications, fields of use, and territories should be limited to be commensurate with the abilities and commitment of licensees to bring the technology to market expeditiously.

For example, patent claims to gene sequences could be licensed exclusively in a limited field of use drawn to development of antisense molecules in therapeutic protocols. Independent of such exclusive consideration, the same intellectual property rights could be licensed nonexclusively for diagnostic testing or as a research probe to study gene expression under varying physiological conditions.

License agreements should be written with developmental milestones and benchmarks to ensure that the technology is fully developed by the licensee. The timely completion of milestones and benchmarks should be monitored and enforced. Best practices provide for modification or termination of licenses when progress toward commercialization is inadequate. Negotiated sublicensing terms and provisions optimally permit fair and appropriate participation of additional parties in the technology development process.

Funding recipients and the intramural technology transfer community may find these recommendations helpful in achieving the universal goal of ensuring that public health consequences are considered when negotiating licenses for genomic technologies.

PHS [The Public Health Service] encourages licensing policies and strategies that maximize access, as well as commercial and research utilization of the technology to benefit the public health. For this reason, PHS believes that it is important for funding recipients and the intramural technology transfer community to reserve in their license agreements the right to use the licensed technologies for their own research and educational uses, and to allow other institutions to do the same, consistent with the Research Tools Guidelines.

Available in full at: http://ott.od.nih.gov/policy/lic_gen.html.

Policies similar to NIH's *Best Practices* are in place for the International HapMap Project, the goal of which is to compare the genetic sequences of different individuals to identify chromosomal regions where genetic variants are shared. By making this information freely available, the project aims to help biomedical researchers find genes involved in disease and responses to therapeutic drugs.

In addition, the Genetic Association Information Network project, a public-private partnership between NIH and the private sector, also uses the approach set out in the *Best Practices* document. Collaborators have adopted an intellectual property policy that all of the data from this effort will be placed in a public database so that they can be shared with other investigators. This prevents third parties from taking inappropriate ownership.

To optimize the number of new products that will reach the market, NIH licenses its technology through nonexclusive licenses, exclusive licenses in narrowly defined fields of use, or exclusive licenses. Since 1990, the agency has also required that its licensed technology be made available for non-commercial research by for-profit, Government, and nonprofit researchers. Most NIH patent commercialization licenses are nonexclusive (80 percent), some are co-exclusive, and the few that are exclusive, in areas such as therapeutics or vaccines, are quite narrow (limited to a particular field of use, disease indication, or technology platform). As noted earlier, NIH grants exclusive licenses when it is a reasonable and necessary incentive for the licensee to risk capital and expenditures to bring the invention to practical application.[167]

Under the Bayh-Dole Act, NIH may limit a grantee's right to elect title or NIH may elect title itself "in exceptional circumstances when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives" of the Bayh-Dole Act.[168] If NIH believes such "exceptional circumstances" are involved, it must file a statement with the Secretary of

[167] Driscoll, C., Director, Technology Transfer Office, National Human Genome Research Institute (NHGRI). Presentation to SACGHS. March 27, 2007.
[168] 35 U.S.C. 202.

Commerce justifying its determination of exceptional circumstances.[169] If the Secretary of Commerce finds that the determination of exceptional circumstances "is contrary to the policies and objectives of this chapter or otherwise not in conformance with this chapter, the Secretary shall so advise the head of the agency concerned and the Administrator of the Office of Federal Procurement Policy, and recommend corrective actions."[170] If the Secretary of Commerce agrees with the determination, the grantee can file an appeal with the U.S. Court of Federal Claims, and the determination of exceptional circumstances shall be held in abeyance until the appeal is resolved.[171] Some legal scholars have argued that the requirement that agencies withhold patenting rights only "in exceptional circumstances" is too burdensome, potentially deterring NIH and other agencies from invoking the procedure when needed.[172] These scholars call for deleting this language from the statute, so that agencies such as NIH will have more discretion in controlling patenting rights.[173] NIH would use its discretion judiciously, they argue, because the agency recognizes the value of patenting in promoting commercial development of technology and would only withhold patenting rights from a grantee when it served the aims of the Bayh-Dole Act.[174] These legal commentators also recommend allowing research on the subject grant/award to proceed during the appeal of a determination.[175]

In certain limited circumstances, in addition to the Government's standard grant of license rights under the Bayh-Dole Act to practice or have practiced for or on behalf of the United States any subject invention throughout the world, the Bayh-Dole Act permits a Federal agency to "march-in" and secure broader rights from the holder of a patent that was funded by the Federal Government.[176] The four limited circumstances under which the Government can use its "march-in" rights are as follows: (1) when the grantee or

[169] Ibid.
[170] Ibid.
[171] Ibid; 35 U.S.C. 203(b).
[172] Rai, A.K., and R.S. Eisenberg. (2003). Bayh-Dole reform and the progress of biomedicine. *Law & Contemporary Problems* 66:289.
[173] Ibid.
[174] Ibid.
[175] Ibid.
[176] 35 U.S.C. § 203.

contractor has not taken and is not expected to take within a reasonable time effective steps to achieve practical application of the subject inventions; (2) when such action is necessary to alleviate health or safety needs that are not reasonably satisfied by the contractor, assignee, or licensee; (3) when such action is necessary to meet requirements for public use that are not reasonably satisfied; and (4) when such action is necessary to provide preference for United States industry or "because a licensee of the exclusive right to use or sell any subject invention in the United States is in breach of such agreement."[177] In using its "march-in" authority, the Government can either require the grantee or contractor to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant(s) or the Government can grant such a license itself.[178]

March-in has been proposed as an option to remedy any potential problems that arise in patient access to genetic diagnostics.[179] However, commentators have questioned the usefulness of the procedure. As with the administrative procedures involved in declaring exceptional circumstances, the administrative procedures involved in invoking march-in rights are viewed by some legal commentators as overly stringent.[180] In fact, "the administrative obstacles are sufficiently cumbersome that NIH has never exercised these rights."[181] Then-deputy director of the NIH OTT Barbara M. McGarey made a similar observation in an article on the CellPro petition for march-in: "The CellPro Petition also highlights the unwieldy nature of the march-in administrative process."[182] McGarey and her co-author later elaborate that if a situation arose where march-in was justified by a health care emergency, "the administrative process would likely not be expeditious enough to address the situation."[183]

[177] 37 C.F.R. 401.14.
[178] 37 C.F.R. 401.14(j).
[179] Holman, C. H. Recent legislative proposals aimed at the perceived problem of gene patents. American Bar Association Biotechnology Section, available at http://www.abanet.org/scitech/biotech/pdfs/recent_legislative_chris_holman.pdf
[180] Rai, A.K., and R.S. Eisenberg, op. cit.
[181] Ibid.
[182] McGarey, B. M., Levey, A.C. (1999). Patents, products, and public health: an analysis of the CellPro march-in petition. *Berkeley Technology Law Journal* 14:1095-1116. p. 1109-1110.
[183] Ibid., p. 1110.

Given the administrative hurdles involved with march-in, McGarey and her coauthor suggest that alternative laws would be more effective if there is a public health need for an invention.[184] For instance, under 28 U.S.C. § 1498, the government can practice an invention without a license if that practice is by or for the United States.[185] Despite the drawbacks of invoking the march-in provision—including the possibility that its frequent use would discourage licensing of federally funded inventions—the authors recognize its value as a "threat . . . to federal funding recipients to ensure appropriate commercialization of the inventions."[186]

Other commentators have proposed changes to the march-in procedures to lessen the administrative hurdles it involves. Arti Rai and Rebecca Eisenberg called for changing "the requirement that march-in authority be held in abeyance pending exhaustion of all court appeals by the government contractor . . . ."[187] These legal scholars argue that allowing agencies to proceed with march-in more expeditiously seems appropriate, given that march-in in some cases may be needed to alleviate health or safety needs.[188]

In October 2008, in response to a congressional mandate, the U.S. Government Accountability Office initiated a study to address the following questions:

1. What policies and procedures have NIH, DOD [Department of Defense], DOE [Department of Energy], and NASA [National Aeronautics and Space Administration] established to determine whether march-in rights under the Bayh-Dole Act should be exercised?
2. To what extent have these agencies exercised the march-in rights under the Act?

[184] Ibid.
[185] Ibid.
[186] Ibid., p. 1096.
[187] Ibid.
[188] Ibid.

3. What barriers, if any, have these agencies encountered in the exercise of march-in rights?

Association of University Technology Managers

Other groups have issued guidance in technology transfer practices. In 2007, the Association of University Technology Managers (AUTM) issued points to consider in managing intellectual property in the academic environment (see Box B).

Box B: AUTM "In the Public Interest: Nine Points to Consider in Licensing University Technology"

Point 1: Universities should reserve the right to practice licensed inventions and to allow other nonprofit and governmental organizations to do so.

Point 2: Exclusive licenses should be structured in a manner that encourages technology development and use.

Point 3: Strive to minimize the licensing of "future improvements."

Point 4: Universities should anticipate and help to manage technology transfer related conflicts of interest.

Point 5: Ensure broad access to research tools.

Point 6: Enforcement action should be carefully considered.

Point 7: Be mindful of export regulations.

Point 8: Be mindful of the implications of working with patent aggregators.

Point 9: Consider including provisions that address unmet needs, such as those of neglected patient populations or geographic areas, giving particular attention to improved therapeutics, diagnostics and agricultural technologies for the developing world.

Source: Available in full at: http://www.autm.net/AM/Template.cfm?Section=Nine_Points_to_Consider.

Literature Review

There is a paucity of data specifically addressing the role of patents and licenses on patient and clinical access to diagnostic genetic tests. Relevant studies are described below.

In 2002, Merz et al.[189] reported that approximately 30 percent of laboratories discontinued or did not offer the test for hereditary hemochromatosis (HH), because the patent for the test was exclusively licensed to SmithKline Beecham Clinical Laboratories. Merz and colleagues concluded that this licensing situation had implications for test quality and patient access, because there was little opportunity for validation and confirmation studies and limited ability to incrementally innovate or develop clinical expertise.

However, subsequent analysts have written that "it is not clear whether the respondents inhibited by patent protection in Merz *et al's* study were labs carrying out evaluative research or those in the business of imitating patented tests."[190] Liddell et al. wrote:

> Based on reports of this kind, it is often assumed that the patent system is detrimental for clinical genetics. The articles overlook four points. First, it is possible that laboratories discontinued the HFE genetic test for haemochromatosis not due to the cost of sub-licences, but due to the test's low clinical utility. Secondly, there are certain technical advantages of centralising the provision of genetic tests with a small number of laboratories. It is far easier to ensure a consistent quality of testing across one or two labs, than to produce a standardised kit suited to wide deployment. This is particularly so for complex tests, which may be difficult to turn into a standardised kit which can be used in multiple labs,

[189] Merz, J., Kriss, A., Leonard, D., and M. Cho. (2002). Diagnostic testing fails the test: The pitfalls of patents are illustrated by the case of haemochromatosis. *Nature* 415:577.
[190] Liddell, K., Hogarth, S., Melzer, D., and R.L. Zimmern. (2008). Patents as incentives for translational and evaluative research: The case of genetic tests and their improved clinical performance. *Intellectual Property Quarterly* 3:286-327.

> and which may best be carried out by major reference laboratories until consistent sampling procedures are established. One respondent also pointed out that monopoly provision of genetic services does not run wholly against the grain. The 'reference lab' model is well accepted as a way of improving the quality of rare disease genetic tests.[191]

In 2003, Mildred Cho and colleagues[192] surveyed directors of laboratories conducting clinical genetic testing. The key findings of their survey were as follows:

> Twenty-five percent of respondents reported that they had stopped performing a clinical genetic test because of a patent or license. Fifty-three percent of respondents reported deciding not to develop a new clinical genetic test because of a patent or license. In total, respondents were prevented from performing 12 genetic tests, and all of these tests were among those performed by a large number of laboratories. We found 22 patents that were relevant to the performance of these 12 tests. Fifteen of the 22 patents (68%) are held by universities or research institutes, and 13 of the 22 patents (59%) were based on research funded by the United States Government.[193]

The survey found little support for the value of patenting among laboratory directors, and the authors concluded that "patents and licenses have a significant negative effect on the ability of clinical laboratories to continue to perform already-developed genetic tests" and continued by remarking that "we do not know whether patients who were denied access to these tests had testing performed by another laboratory…. Practitioners in the United States who perform these tests on a daily basis overwhelmingly feel that costs, both to laboratories and to patients, have been increased. Such increases can only lead to limited access."[194]

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[191] Ibid., p. 293.
[192] Cho, M.K., et al. (2003). Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnosis* 5(1):3-8.
[193] Ibid., p. 3.
[194] Ibid., p. 8.

As mentioned previously, in 2004, Jensen and Murray[195] identified 4,270 U.S. patents that refer to at least 1 human gene in the patent claims and concluded that one-fifth of known human genes are referred to in patent claims.

A 2007 article by Kaye et al. noted problems in developing a genetic test for sudden cardiac death, writing that the Oxford Genetics Knowledge Park was unable to conduct research on such a test because of the licensing provisions.[196] However, in 2006, the Intellectual Property Institute found that only a small fraction of researchers had been denied access to genetic technology. It concluded that the research exemption in the United Kingdom was effective.[197]

In 2005 Paradise et al.[198] reviewed DNA patents associated with nine diseases. Their selection criteria were outlined as follows:

> [H]uman gene patents that represented a range of genetic diseases—from single gene to multigene disorders, from diseases where the genetic predisposition has been identified to those where the causal nexuses are still being identified. We used the term "human gene patent" to include not only patents on complete human gene sequences, but patents that cover any human genetic material, such as mutations in a gene, or diagnostic methods that utilize human genetic material that would effectively preclude the use of that material by others. We chose genetic diseases that were subject to public attention and for which problems in gene patents could potentially have an impact on research and health care.[199]

[195] Jensen, K., and F. Murray. (2005). Intellectual property landscape of the human genome. *Science* 310:239-240.
[196] Kaye, J., Hawkins, N., and J. Taylor. (2007). Patents and translational research in genomics. *Nature Biotechnology* 25(7):739.
[197] Intellectual Property Institute. (2006). *Patents for Genetic Sequences: The Competitiveness of Current UK Law and Practice.* London: Intellectual Property Institute.
[198] Paradise, J., Andrews, L., and T. Holbrook. (2005). Intellectual property. Patents on human genes: an analysis of scope and claims. *Science* 307(5715):1566-1567.
[199] Ibid., p. 1566.

Their approach was to have a group of experts (in patent law, science, and relevant technologies) make independent judgments about patents covering 74 gene sequences, identifying "problem" patents for which, in their judgment, at least one of the patent criteria (novelty, utility, nonobviousness, enablement, full written description, and definiteness) was not fully met. The reviewers found that 38 percent of the patents were problematic, with written description and enablement/utility being the most frequent problems.

A 2005 licensing survey reviewed ownership of DNA patents and found that, among the top thirty entities holding the largest number of DNA patents, the number one patent holder was the University of California, followed by the U.S. Government (with most of the Government's patents resulting from NIH's intramural research program). These top thirty entities own 28 percent of all DNA patents issued by USPTO through September 14, 2005. Many of the top 30 DNA patent holders in this group were universities.[200] Academic institutions with the greatest number of DNA patents report that they generally include provisions permitting noncommercial research when they license those patents.

In May 2006, Caulfield and colleagues held a workshop in Banff, Alberta, to review evidence about gene patenting and public policy. This included a survey of policy reports, influential articles, policy changes, and guidelines for patenting and licensing issued by various organizations and governments. Although the Banff workshop was not about diagnostics, many of the issues cited in the policy reports being reviewed were about diagnostics (heritable breast cancer risk was far and away the most frequently mentioned, but also mentioned were HH, Alzheimer's disease [AD], Canavan disease, Huntington disease, heritable colon cancer, fragile X syndrome, muscular dystrophies, spinocerebellar ataxia [SCA], and others). An article resulting from that conference concluded that a:

[200] Pressman, L., Burgess, R., Cook-Deegan, R.M., McCormack, S.J., et al. (2006). The licensing of DNA patents by US academic institutions: an empirical survey. *Nature Biotechnology* 24(1):31-39.

> systematic review of the content and timing of major policy documents highlights the fact that policy activity has been largely stimulated by a convergence of a general social unease, the emergence of preliminary data and literature on the possible adverse practical ramifications of gene patents and several high-profile patent protection controversies.[201]

One issue that has been plaguing efforts to assess varying impacts of gene patents and licensing on access and cost is reliable and consistent data. Huang and Murray have noted the reliance of scholars on evidence from individual cases illustrating aggressive enforcement of gene patents, which do not provide a useful picture of the extent of aggressive practices across a wide variety of patents and patent holders:[202]

> A better approach would be to rely on large-scale empirical studies. However, several inherent challenges account for why such studies have not been forthcoming until now. First, until the recent documentation of the patent landscape of the human genome (Jensen & Murray, 2005), systematic data on private (patented) genetic knowledge was limited. Second, even with such data, traditional approaches cannot estimate the causal impact of patenting on the public knowledge stream: given the possible variations in knowledge associated with patented and unpatented genes, simple comparisons are uninformative. A third issue further confounds the problem: confusion as to whether the public and private knowledge streams should be defined by different types of knowledge (basic v. applied), the organization of knowledge production (academia v. industry), or the institutional sphere defining knowledge disclosure, access and accumulation (public commons v. private property). Finally, management theory has no synthetic framework in which to analyze disparate evidence on the relationship between the public and private knowledge streams.[203]

[201] Caulfield, T., Cook-Deegan, R.M., et al. (2006). Evidence and anecdotes: an analysis of human gene patenting controversies. *Nature Biotechnology* 24(9):1091-1094.
[202] Huang, K.G., and F.E. Murray. (Forthcoming). Does patent strategy shape the long-run supply of public knowledge? Evidence from human genetics. *Academy of Management Journal.*
[203] Ibid., p. 4.

Huang and Murray analyzed the effect of gene patents on the rate at which scientists contribute to the "follow-on stream of public knowledge building on the gene papers, relying on several methodological and econometric advances."[204] They used publication citations to each gene paper as a proxy for public knowledge accumulation, noting that citations do not capture accumulation of nondisclosed knowledge. Their goal was to understand how patent strategies, such as scope, ownership, landscape, and commercial relevance of patented private knowledge, affect public knowledge. They concluded that "follow-on genetic researchers forego about one in ten research projects (or more precisely research publications) through the causal negative impact of the gene patent grant."[205] Thus, gene patents decrease public genetic knowledge, an effect that is amplified with broader patent scope, private-sector ownership, the complexity of the patent landscape, and the gene's commercial relevance.

A group of researchers recently looked at the effect of patenting on the ability of agricultural biologists to obtain research tools from fellow scientists at other institutions.[206] Research tools are biological materials such as DNA molecules and cell lines that are used in the course of an investigator's experiments; among the agricultural biologists described in this study, isolated gene molecules, plasmids, and vectors were the most commonly exchanged tools. The investigators report that many agricultural biologists believe that the sharing of research tools has been complicated not by patents themselves, but by the Material Transfer Agreements (MTAs) associated with the patents.[207] When providing a research tool to another institution, universities rely on MTAs to protect intellectual property rights associated with the tool.[208] The study authors found that these MTAs have "increased the frequency of cases of delayed or blocked access to needed research tools."[209] Problems in obtaining research tools, in turn, caused

[204] Ibid., p. 23.
[205] Ibid., p. 40.
[206] Lei, Z., Juneja, R., and B.D. Wright. (2009). Patents versus patenting: implications of intellectual property protection for biological research. *Nature Biotechnology*: 27(1): 36-40.
[207] Ibid.
[208] Ibid.
[209] Ibid., p. 39.

an average delay in research of 8.7 months.[210] In some cases, difficulties caused researchers to use less effective tools or to abandon projects altogether.[211] These research delays and problems could delay research discoveries and any technologies based on those discoveries. If such delays occurred in human genetics research, the delays could slow the development of genetic tests, which in turn would delay patient access to such tests.

The Uniform Biological Material Transfer Agreement, developed in part by NIH, is meant to facilitate the easy exchange of research tools.[212] The study authors found support among agricultural biologists for the widespread use of this agreement as a means of addressing the problems identified in the study.[213]

Litigation Literature

- Merz and Henry found that interferences[214] are particularly likely in molecular biological inventions, presumably because of many close "races" for genes and proteins that are associated with biological pathways and diseases.[215]

- In 2008, Holman[216] conducted a study to identify all instances in which a human gene patent was asserted in an infringement lawsuit. He identified 31 human gene patent litigations dating back to 1987. Only 7 of the 31 lawsuits involved patents

[210] Ibid.
[211] Ibid.
[212] Information on the UMBTA can be found at http://www3.niaid.nih.gov/about/organization/odoffices/omo/otd/UBMTA.htm.
[213] Lei, Z., Juneja, R. and B.D. Wright, op. cit.
[214] The United States is the last remaining country with a "first-to-invent" system rather than a "first-to-file" system. One question that might be asked is whether there is an effect of this fundamentally different standard and if so, what that effect is. In addition, although many urge the harmonization of international patent laws as a means of decreasing administrative and regulatory burdens, it is unclear whether or not the differences help or hinder innovation. Also, one major emerging economic power, Brazil, has an extremely strong intellectual property system (using only novelty as criteria for patent grant), even while their government is the leader in invocation of the Agreement on Trade Related Aspects of Intellectual Property Rights **(**TRIP) flexibilities such as compulsory licensing.
[215] Merz, J.F., and M.R. Henry. (2004). The prevalence of patent interferences in gene technology. *Nature Biotechnology* 22(2):153-154.
[216] Holman, C.M. (2008). "Trends in human genome patent litigation." *Science* 32:198-200.

identified by Murray and Jensen. Only 5 of the cases involved diagnostics all of which were settled before any substantive decision. The authors conclude that these patents are not litigated frequently compared to other biotechnology patents, and when they are, they settle early.

- In a 2008 study, Mills and Tereskerz found a similarly small number and absolute percent of litigations for DNA-patents.[217]

Previous Policy Studies

Four previous policy reports addressing the issue of patenting genes or biotechnology inventions merit attention, because they contain sections specific to genetic tests. These studies were conducted by the Nuffield Council on Bioethics (United Kingdom), the Australian Law Reform Commission (ALRC), the National Research Council (NRC) (United States), and the Organisation for Economic Co-Operation and Development (OECD).

Nuffield Council. The Nuffield Council on Bioethics, which is funded by two nonprofit charities and the U.K.'s Medical Research Council, issued *The Ethics of DNA Patenting* in 2002. The report urged raising the bar for obviousness and utility when granting DNA patents in the United Kingdom, as well as narrowing definitions of uses covered by patent claims. It also raised the possibility of compulsory licensing of diagnostic patents so that public health needs would be met.[218]

Australian Law Reform Commission. ALRC, an advisory body to the government, issued a major report addressing biotechnology and patents, devoting more attention to gene patents than any other government group. [219] With regard to Australian law and

[217] Mills, A.E. and P. Tereskerz. (2008). DNA-based patents: an empirical analysis. *Nature Biotechnology* 26(9):993-995.
[218] Nuffield Council, 2002, pp. 48-56.
[219] ALRC. *Genes and Ingenuity: Gene Patenting and Human Health June 2004*. Australia: SOS Printing Group, http://www.austlii.edu.au/au/other/alrc/publications/reports/99/index.html.

practices, the final 2004 ALRC report found "no clear evidence of any adverse impact, as yet, on access to medical genetic testing, the quality of such testing, or clinical research and development."[220] The report noted, however, that "some people in the Australian public health sector harbor genuine and serious concerns about the implications of gene patents. . . . There are arguments suggesting that the exclusive licensing of patents relating to medical genetic testing may have adverse consequences, depending on the behavior of licensees."[221]

Organisation for Economic Co-operation and Development. OECD, a forum in which the governments of 30 countries work together to address the economic, social, and environmental challenges of globalization, issued *Guidelines for the Licensing of Genetic Inventions* in 2006.[222] These guidelines were developed in response to a 2002 workshop that investigated the impact of patents and licensing strategies of genetic inventions on access to information, products, and services for researchers, clinicians, and patients. Although the bulk of the evidence indicated that the intellectual property system was functioning as intended, there were some underlying concerns with respect to potential issues with access to diagnostic genetic tests. Broadly speaking, the OECD guidelines support licensing strategies that foster innovation, promote dissemination of information and developments related to genetic inventions, and encourage access to and use of genetic inventions for the improvement of human health.

In October 2003, the **Federal Trade Commission** issued a report, *To Promote Innovation: the Proper Balance of Competition and Patent Law and Policy*,[223] suggesting that broad patents may be having anti-competitive effects and blocking innovation in certain high-technology industries, such as computers and biotechnology. The report makes a number of recommendations aimed at restoring the balance between competition and patent policy and improving patent quality (e.g., by reducing the number of obvious

[220] Ibid., p. 503, point 20.72.
[221] Ibid., p. 504, point 20.77.
[222] See http://www.oecd.org/document/26/0,3343,en_2649_34537_34317658_1_1_1_1,00.html.
[223] Federal Trade Commission. (2003). *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy*, http://www.ftc.gov/os/2003/10/innovationrpt.pdf .

patents). The report also recommends new mechanisms to make it less onerous to challenge invalid patents and new procedures to allow increased access to pending patents for the purpose of business planning and avoiding infringement.

National Research Council. As discussed previously, NRC's 2006 report, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health*, was an immediate precursor to the current SACGHS study. Most of the NRC report and recommendations focus on the impacts of intellectual property law and policies on research, but the report also included a section on clinical testing that led to a recommendation with direct bearing on diagnostics. The recommendation calls for Congress to consider a limited statutory exemption from patent infringement liability for clinical verification testing.

> Recommendation 13: Owners of patents that control access to genomic- or proteomic-based diagnostic tests should establish procedures that provide for independent verification of test results. Congress should consider whether it is in the interest of the public's health to create an exemption to patent infringement liability to deal with situations where patent owners decline to allow independent verification of their tests.[224]

The NRC committee commissioned three lines of inquiry, and staff conducted additional research. The committee drew on the DNA Patent Database for aggregate data on U.S. patents, worked with USPTO's Examining Group 1600, which reviews patent applications in the areas of biotechnology, pharmaceuticals, and organic chemistry, and commissioned a survey of scientists that explored research access to patented materials.[225] The NRC committee also performed its own analysis of specific cases, including some U.S.-European comparisons. Its strong emphasis, however, was on

[224] NRC, 2006, op. cit., p. 18.
[225] Walsh, J.P., Cho, C., and W.M. Cohen. (2002). View from the bench: Patents and material transfers. *Science* 309**:**2002-2003. Walsh, J.P. Cho, C., and W.M. Cohen. Final Report to the National Academy of Sciences' Committee on Intellectual Property Rights in Genomic and Protein-Related Inventions Patents, Material Transfers and Access to Research Inputs in Biomedical Research. September 20, 2005

research, rather than on clinical use, except for clinical case studies of genetic testing for the *BRCA* genes, Canavan disease, and Huntington disease.

The NRC, Nuffield, OECD, and ALRC reports share an analytical framework, as does most of the literature on the patenting and licensing of genetic diagnostics. The reports accept the value of the patent system and cite its positive impacts on innovation generally. None of the reports make a compelling case that patenting was either necessary or sufficient to develop a particular genetic test. Rather, these studies indicate that the main value of biotechnology patents appears to be foreclosing the possibility that "free riders" will benefit from a company's initial research and development investments for creating and commercializing platform technologies or therapeutics. In these areas, a track record of more extensive litigation suggests that the patent system has been used to protect inventions, but it is not clear that patents are needed in order for innovation to move forward. However, none of the studies argue for eliminating patents on DNA molecules, even in the context of genetic testing.

International Comparisons

As part of its fact finding, SACGHS convened a roundtable in July 2007 to gather background information on the gene patenting and licensing practices of other countries. Presenters suggested that in most developed countries, patent policies support gene patents but cautioned that they must be properly managed. There has been little discussion of patent reform, *per se*, or of the need for legislation to remedy problems arising from gene patenting. Discussions at the international level have focused on licensing practices. There is a general view that, even though the law does not require it, it is preferable for gene patents to be nonexclusively licensed, although exclusive licenses might be justified in certain circumstances, for example, to accommodate health care providers so that they can control the availability of treatment. Many concerns at the international level are similar to those in the United States—for example, researcher

access, follow-on research, and the development of alternative clinical therapies or diagnostic kits.

Currently, intellectual property law is regulated through a combination of international organizations or treaties, regional treaties, regional instruments, bilateral agreements, and national laws.[226] Internationally, the World Intellectual Property Organization (WIPO) and the 1994 World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) have the most widespread influence. WIPO administers previously established intellectual property treaties in addition to newer agreements, including most notably the 1970 Patent Cooperation Treaty. Under this treaty, inventors can use a standardized application to file patents in all contracting countries (128 total in 2005).[227] Patents are still granted by each individual nation, however, and as such are subject to national patent law. It needs to be emphasized that national laws on patentability and infringement differ from one another significantly, which makes international comparisons on issues related to patent law (as opposed to licensing practices) somewhat difficult.

As gene patenting has become an international concern, numerous international initiatives have focused on this question. UNESCO (the United Nations Educational, Scientific and Cultural Organization) released the Universal Declaration on the Human Genome and Human Rights in 2007, and the Human Genome Organization Ethics Committee released statements on Patenting of DNA sequences in 1995 and 2000. OECD convened an Expert Workshop on Genetic Inventions, Intellectual Property Rights and Licensing Practices in 2002 and more recently released licensing guidelines for genetic inventions. The Nuffield Council on Bioethics released a discussion paper on the ethics of patenting DNA also in 2002, as did the Commission on Intellectual Property Rights, established by the British government to determine the effects of intellectual property rights on developing countries. ALRC also undertook an analysis of gene patents in

[226] UNCTAD/ICTSD. (2003). I*ntellectual Property Rights: Implications for Development*, http://www.iprsonline.org/unctadictsd/policyDpaper.htm.
[227] Salmon, P.E. (2008). *A Short Guide to International IPR Treaties*, http://usinfo.state.gov/products/pubs/intelprp/guide.htm.

Australia, released in 2004. Finally, the World Health Organization has released a report on *Genetics, Genomics, and the Patenting of DNA*, and there have been numerous academic publications relating to gene patents.

In general, most countries have exemptions to patentability. In Europe, national legislation follows the European Patent Convention, and exclusions from patentability typically include discoveries, aesthetic creations, scientific theories, mathematical methods, computer programs, and presentations of information. Other subject matter that may fulfill the requirements for patentability but is nonetheless ineligible for patents may include methods for treatment of humans or animals by surgery or therapy, diagnostic methods, inventions whose commercial exploitation would be contrary to morality or public order, and plant or animal varieties and biological processes essential for their production.

Similar rules are found elsewhere. Most countries have a public order exemption (except the United States, Canada, and Australia), and most have determined that inventions relating to medical treatments are not patentable (although Canada deems diagnostic procedures patent-eligible). Most allow for some form of compulsory licensing (in Canada, Australia, and the United States, there is only a government use provision); all allow for compulsory licenses against anti-competitive activity.

Most countries have research exemptions for those conducting research on the nature of the invention or to improve it, and most countries have an exemption to satisfy regulatory requirements. In some countries, such as Germany and France, the research exemption extends to clinical trials.[228] Canada, Australia, and the United States seem to have the fewest exemptions.

[228]Centre for Intellectual Property Policy (CIPP). (2004). *The Research or Experimental Use Exception: A Comparative Analysis*. http://www.cipp.mcgill.ca/en/news/newsletter/8/.

The United States has the strictest test regarding utility, requiring that an invention have a specific, substantial, and credible utility.[229] For all other countries, demonstration that the invention works and can be made is sufficient to establish utility.[230]

In terms of inventiveness or nonobviousness, the European Patent Office's (EPO's) problem/solution test is one of the strictest tests for the inventive step. Non-European countries simply ask whether the invention would have been obvious to someone with knowledge in that technical field. However, the sweep of art considered in determining whether the invention is "novel, not obvious, and useful" is broader in the United States than in Europe. Thus, sometimes the breadth of a patent granted in Europe is broader than the scope of a U.S. equivalent, and sometimes is it narrowed than its U.S. equivalent. With respect to patents claiming DNA sequences, the United States' test for nonobviousness has changed since two seminal cases in the mid-1990s, *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) and *In re Deuel*, 51 F.3d. 1552 (Fed. Cir. 1995). (See the above discussion in the overview of patent law and licensing.)

Some countries provide a grace period for filing a patent application after disclosing an invention. For example, in the United States, if an inventor chooses to first disclose his or her invention in a published article, he or she has a one-year grace period from the date of the publication to file a patent application for the invention; if the inventor has not filed the application after the year has passed, he or she is barred from patenting the invention. Unlike the United States, most foreign countries treat public disclosure of an invention as a bar against obtaining a patent. In these countries, one must first seek the patent before publicly disclosing the invention—otherwise, a patent is not available. The reasons these countries require that the invention be disclosed to the patent office first is because they have a "first-to-file" rule for determining inventorship. The United States, on the other hand, awards patents to those who are the first to invent. Because of the U.S. policy of first to invent, it is the only major country that has a rule stating that if there is a dispute

[229] CIPP. (2005). *Genetic Patents and Health Care in Canada: An international Comparison of the Patent Regimes of Canada and Its Trading Partners*. Prepared for the Canadian Biotechnology Advisory Committee. January.
[230] Ibid.

between two people who filed patents at the same time, the courts must decide who invented it first through an interference proceeding.

Most countries allow patents to be challenged, either through the patent office itself or through public hearings, and patents can be challenged before or during infringement action.

All countries reviewed except Brazil seem to allow gene patenting, although in many cases the status of gene patents is ambiguous. Few countries have enacted legislation dealing directly with gene patenting, and in such cases prior art and the scope of interpretation are crucial to determining the stringency of gene patenting requirements. Some countries, like the United States, rely on a combination of prior art and guidelines, without specific gene patent regulation. Other countries, such as Germany and France, limit the scope of patents to the utility recited in the patent.

There is an opposition process in Europe that does not exist in the United States, although the United States does allow re-examination. In Europe, when a patent is published, there is a period of time during which outside parties can state that they think it is too broad and that more information must be taken into consideration. This initiates a proceeding to look at the patent again in light of the new information contributed by these parties. This process led to the dramatic narrowing of the *BRCA1* patent in the European Union from the entire gene to three specific mutations that are highly prevalent in some Ashkenazi Jewish families. However, a primary reason for the narrowing of the patent in Europe was that the European patent application misstated parts of the *BRCA* sequence. The EPO Appeals Board recently amended a Myriad patent claiming a diagnostic process for breast cancer but limited the patent to frameshift mutations.[231] The patent does not claim the *BRCA1* gene or mutations of it.[232]

[231] Ray, T. (2008). EPO's decision to amend Myriad's BRCA1 IP may create more uncertainty for Euro labs. *Pharmacogenomics Reporter*, http://www.pgxreporter.com/issues/6_47/features/151068-1.html?CMP=OTC-RSS.
[232] Ibid.

In 2008, the European Society of Human Genetics (ESHG) recommended "limiting the breadth of the claims in genetic patents and, more practically, to reduce the number of patents by limiting the patentable subject matter, thereby improving the quality of the patents that will eventually be granted."[233] Moreover, ESHG wrote that it "sees no harm in the patenting of novel technical tools for genetic testing (e.g., PCR or chip technologies), as they can promote investment and still allow for invention around them." The group supports the OECD guidelines, which urge that licenses should be nonexclusive and easily obtainable, both in practical and in financial terms. It recommends:

> To promote this, the practical exploration of alternative models for licensing, like patent pools and clearinghouses, is a prerequisite. To better track developments in this field, the establishment of a voluntary reporting system, whereby geneticists could report on any issues related to new and/or old patents or licences in the light of service provision to patients, would be worthwhile. [234]

Although some differences remain in specific countries over whether or not genes can be patented, the international consensus is that they can be. As long as the DNA sequence is novel and the other criteria of patentability are also met—namely utility and nonobviousness—the sequence of the DNA itself can be patented.[235] Like the United States, other countries often limit the patenting of DNA to the isolated, purified form of the molecule.[236]

Under Article 27 of TRIPS, members are required to make patents available in all fields of technology, although they may elect to exclude from patentability diagnostic methods

[233] Ayme, S., Matthijs, G., and S. Soini, on behalf of the ESHG Working Party on Patenting and Licensing. (2008). Patenting and licensing in genetic testing Recommendations of the European Society of Human Genetics. *European Journal of Human Genetics* 16:405-411.
[234] Ibid., p. S3.
[235] Organization for Economic Co-operation and Development. (2002). *Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies*, http://www.oecd.org/dataoecd/42/21/2491084.pdf.
[236] Ibid.

for the treatment of humans, plants, and animals other than microorganisms, and a few other types of technology.[237] TRIPS does not state that members may exclude DNA sequences from patentability.[238] Therefore, it seems reasonable to infer that if the United States or another country prohibited DNA patents it would be violating TRIPS. Nonetheless, some legal scholars have argued that prohibiting DNA patents may not violate TRIPS.[239]

There have not been any cases interpreting TRIPS as requiring patents on DNA. If a member of WTO were to deny patents on DNA on the ground that it is a natural product, it is conceivable that another member state might challenge that as a violation of the Agreement. But until that happens, and there actually is a case, it is not clear how TRIPS would be interpreted.

Case Studies

SACGHS enlisted the resources of Duke University's Institute for Genome Sciences and Policy Center for Genome Ethics, Law, and Policy (GELP), directed by Dr. Robert Cook-Deegan, in December 2006. GELP faculty, postdoctoral fellows, research associates, and graduate students conducted case studies that analyzed the experience of laboratories, physicians, and patients with patented or unpatented genetic tests for 10 medical conditions: heritable breast and colon cancers, HH, hearing loss, cystic fibrosis (CF), AD, SCA, Long QT syndrome (LQTS), Canavan disease, and Tay-Sachs disease. The Center also conducted an analysis of patenting and licensing of genetic diagnostics and wrote a conceptual overview.

[237] Article 27, TRIPS, http://www.wto.org/english/tratop_e/trips_e/t_agm3c_e.htm#5.
[238] Ibid.
[239] Dinwoodie, G.B., and R.C. Dreyfuss. (2004). International intellectual property law and the public domain of science. *Journal of International Economic Law* 7:431 (providing arguments why subject matter exclusions may not violate article 27.1); see also World Health Organization. (2005). *Genetics, Genomics and the Patenting of DNA: Review of Potential Implications for Health in Developing Countries* (noting that "countries are free to judge for themselves whether the excludability of DNA is inferred . . . ."), http://www.who.int/genomics/en/FullReport.pdf.

The Duke GELP team was unable to access the actual licensing agreements (the legal documents specifying licensing terms for patents of interest) for any of the case studies. For the most part, the only information available consisted of data that patent licensors or licensees chose to make public. Although in many cases this information may be sufficient to characterize a patent as "exclusively licensed," the term can be imprecise or even misleading. Moreover, licenses are not always about royalties. They often provide terms for termination of a license, specify conditions under which the invention must be used, set geographic limits for the utilization of an invention, reserve the right to license the invention nonexclusively for nonprofit research, or permit the patent holder to use the invention itself. Although this information is important for assessing the impact of patents on research and clinical access to genetic testing, it is typically not available to the public, and many companies refuse to divulge it.

It is important to note that access to genetic tests may be hindered by high prices, fear of discrimination, difficulty in obtaining the tests, regulatory or certification requirements, lack of coverage by payers or demands by insurance payers for evidence of clinical utility, all of which could be seen to be at work to a greater or lesser extent in one or more of the case studies. Many of these factors are a function of unique aspects of the overall U.S. health care system, rather than a specific function of intellectual property rights. For the purposes of the case studies and this report, "access to genetic testing" is defined conceptually as the number or percentage of people who need a genetic test and are able to obtain it. The parameters of "access" include:

- whether a diagnostic test is available, and whether improvements are also available;
- whether the cost of the test is reasonable to both the provider and patient;
- the quality of the testing services;
- how quickly the test is available following the discovery of the connection between a particular genotype and phenotype, and how rapidly the test evolves and improves with use and future discoveries;
- The existence of mechanisms for payment for the test; and

- the number of distinct test providers that are available.

Factors directly influenced by intellectual property rights include the availability of a test following the discovery of a particular gene or mutation associated with a disease, the number of providers offering a test, and the test price.[240] Other factors that may play an indirect role in access include coverage and reimbursement of a test by private insurers and other third-party payers; the utility of a test for medical decisionmaking, the quality of the testing services, logistical issues,[241] and fear among patients/consumers of genetic discrimination.[242]

Summaries of the case studies appear below; the case studies themselves are in Appendix 1 of this report.

Comparison of Testing for Heritable Breast and Ovarian Cancers and Colon Cancers

Myriad Genetics' diagnostic test for heritable breast cancer is one of the most well-known examples of a patented genetic test that is exclusively licensed to a sole provider. Specific mutations in the *BRCA1* and *BRCA2* genes can dramatically increase an individual's risk for breast and ovarian cancers. Myriad holds rights to broad patents on both of these genes and is the sole provider of full-sequence *BRCA* testing in the United States. In a parallel fashion, specific mutations in several other genes can lead to hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP), both of which result in an inherited strong predisposition to the development of

[240] Other factors can also play a role in test access. For example, certain genetic tests for rare diseases are sometimes available only through research. However, in order to provide test results for clinical purposes, laboratories must be certified by CLIA, and many research laboratories do not have CLIA certification.
[241] Logistical or "hassle" factors in obtaining a test include having to send test samples to a laboratory outside of the facility where the sample is drawn, the negotiation of coverage and reimbursement for a test, lengthy delays in the delivery of test results, or inconclusive test results. These factors may be particularly problematic when there is a sole provider of a particular test.
[242] Fear of possible uses of genetic information has been cited as an impediment to access in the past; however, the enactment of the Genetic Information Nondiscrimination Act of 2008, once fully effective, may address this factor.

colorectal cancer. In contrast to the patents for the *BRCA1* and *BRCA2* genes, the patents for the genes involved in HNPCC and FAP are predominantly held by nonprofit entities and are licensed nonexclusively. Myriad and four nonprofits offer full-sequence analysis of the *APC* gene, associated with FAP, while Myriad, Quest Diagnostics, Huntington Diagnostic Laboratories, and four nonprofits offer full-sequence analysis for three genes involved in HNPCC (*MLH1*, *MSH2*, and *MSH6*). Therefore, the case study comparing genetic testing for familial breast and ovarian cancers and familial colorectal cancers served as a natural experiment in which potential effects of gene patents and licensing strategies on patient and clinical access could be determined.

There is little consistent evidence of a price effect directly related to patents to which Myriad holds exclusive versus nonexclusive rights. The per-unit (per amplicon) test prices for Myriad's *BRCA* full-sequence analysis are lower ($38.05) than for its colon cancer gene tests (FAP: $40.80 and HNPCC: $49.17). Myriad's prices for sequence analysis of the *APC* gene (FAP) are higher than are the prices charged by some nonprofit testing services ($1,795 versus $1,200 to $1,675), but Myriad's service includes rearrangement testing and comparison services that are priced differently by the other providers (an additional $495 to $625; the Mayo Clinic, like Myriad, includes rearrangement testing in its $1,300 sequencing price). Myriad's price is midrange among providers of HNPCC testing ($2,950 for full sequence of three genes and testing for major rearrangements versus a range of $1,800 to $4,464 for sequencing of one, two, or all three of the genes involved), and lower than the HNPCC testing services offered by another for-profit laboratory ($4,760 for sequencing of all three genes; an additional $540 for rearrangement testing for two genes). Therefore, there is no evidence for a meaningful "patent premium" for *BRCA* testing or the conclusion that patenting of the *BRCA* genes have led to prices far above comparable tests for comparable conditions provided by other laboratories.

There has been substantial criticism regarding Myriad's sole provider status for *BRCA1* and *BRCA2* testing. Specifically, there are concerns that Myriad's definition of research

that infringes on its patent rights is too broad. A 2005 Lewin Group report[243] concluded that, based on incentive effect theory, Myriad's exclusivity under the patents on the *BRCA* genes stifled further basic research. However, few empirical data support or refute the Lewin Group's conclusion. Myriad maintains that it has not enforced its patents against researchers, but it has not stated in a written, actionable form that it would not do so, with the exception of a 1999 Memorandum of Understanding with the National Cancer Institute. This ambiguity may be a factor in stifling research, to the extent that any research has been impeded.

A 2003 French study on the cost-effectiveness of full-sequence *BRCA* testing versus other methods stated that monopoly control "may prevent health care systems from identifying and adopting the most efficient genetic testing strategies."[244] The same study found that alternative strategies "would minimize the cost of diagnosis while also ensuring a comparable level of effectiveness to that of applying DS [direct sequencing] to the entire gene."[245] Myriad disputes this contention, and certainly from a clinical standpoint the analysis that the company performs is clearly the optimal strategy. Screening tests, although less expensive, are suboptimal because of their inherent insensitivity. Most clinicians prefer a test with maximal sensitivity.

Similarly, a 2006 study published in the *Journal of the American Medical Association* (*JAMA)* asserted that Myriad's testing strategy missed up to 12 percent of large genomic deletions or duplications.[246] In testimony submitted to a House Judiciary subcommittee in October 2007, Marc Grodman, M.D., chief executive officer of Bio-Reference Laboratories, Inc., and Wendy Chung, M.D., Ph.D., of Columbia University, attributed this deficiency in the test to Myriad's sole provider status and patent monopoly. In her written testimony, Chung asserted the following:

[243] The Lewin Group. (2005). *The Value of Diagnostics: Innovation, Adoption, and Diffusion into Health Care*, pp. 62-63, http://www.socalbio.org/pdfs/thevalueofdiagnostics.pdf.
[244] Sevilla, C., et al. (2003). Impact of gene patents on the cost-effective delivery of health care: The case of *BRCA1* genetic testing. *International Journal of Technology Assessment in Health Care* 19:287-300.
[245] Ibid.
[246] Walsh, T., et al. (2006). Spectrum of mutations in *BRCA1*, *BRCA2*, *CHEK2*, and *TP53* in families at high risk of breast cancer. *Journal of the American Medical Association* 295(12):1379-1388.

> It was only after considerable pressure from the scientific community that the company added methods to detect these deletions, insertions, and re-arrangements in 2006, over 10 years after they first introduced clinical genetic testing, and barred anyone else from performing the tests. In a competitive marketplace, this delay never would have occurred.[247]

Myriad disagrees with this characterization and notes that it launched testing for the five most common rearrangements, accounting for approximately one-third of all rearrangements, in 2002. Myriad also asserts that the rearrangement testing it was conducting at the time would have detected roughly one-third of the "missing" cases reported in the *JAMA* article. The company incorporated more extensive testing for rearrangements in 2006, the same year the *JAMA* article was published. The general trend for all diagnostic genetic testing has been to move toward more comprehensive analyses that detect deletions and rearrangements, and Myriad's actions have been consistent with the general trend. Indeed, in areas where there is no sole provider, there has been a similar lag in detecting deletions and rearrangements. Part of the delay in developing such analyses could reflect increased technical difficulty in testing for deletions and rearrangements.

Myriad's patent enforcement activities have been a source of the majority of the criticism against the company's *BRCA1* and *BRCA2* patents. A 2003 survey of laboratory directors found nine instances of enforcement of the *BRCA* patents by Myriad. This same group reported two instances of FAP patent enforcements and no cases of HNPCC patent enforcement.[248] Of 31 collected gene patent litigation cases, 5 of which were related to

[247] Dr. Chung's testimony appeared as an appendix to the written testimony of Dr. Marc Grodman presented to the House Judiciary Subcommittee on Courts, the Internet and Intellectual Property during a hearing held on October 30, 2007. Testimony is available at http://judiciary.house.gov/hearings/pdf/Grodman071030.pdf.

[248] Cho, M., et al. (2003). Effect of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnostics* 5(1):3-8. NB: FAP and HNPCC "patent enforcements" are more unlikely, given nonexclusive licensing and multiple rights holders.

diagnostics, the *BRCA* genes accounted for 2 cases and colon cancer genes accounted for none.[249]

Myriad's monopoly and enforcement activities may have inhibited research—more clearly, clinical research on the use of genetic testing rather than basic research. Nonetheless, a considerable amount of research has proceeded, and any chilling effect has been at the margins. Myriad states that it has no intention of inhibiting research. Indeed, in most (but not all) instances, it is in Myriad's interest to promote research and application, because Myriad garners profits from any U.S. testing.

Myriad's statements about supporting research, however, have not been issued in the form of a clear written policy that others can act upon when contemplating research that involves making or using *BRCA* sequences covered by Myriad's patents. Such a statement might help to mitigate any chilling effect on research; however, a formal statement also would limit Myriad's legal options should others choose to offer testing that Myriad does not offer. This is a point of contention for opponents of sole-source test providers, because sole providers cannot credibly claim that they support research (and potentially test services they do not offer) while not explicitly stating their policies regarding permission for such activities without incurring patent infringement charges.

Finally, Myriad's monopoly on *BRCA1* and *BRCA2* gene testing may have increased the incentive to advertise directly to consumers. Although such advertising may have prompted overuse or misuse of the tests, it also publicized the availability of the test to prospective users who might not otherwise have learned of it. On the other hand, one can make a strong case that direct-to-consumer marketing would be more widespread where there is competition and thus where advertising could be seen as a more important tool. It also has been argued that a centralized testing service offers additional benefits to consumers, including Myriad's ability and willingness to provide free testing to first-

[249] Holman, C.M. (2007). The impact of human gene patents on innovation and access: A survey of human gene patent litigation. *UMKC Law Review* 76(2):295-361, at 347-348. Draft available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1090562.

degree relatives once a mutation has been identified in order to further characterize uncertain variants.

Alzheimer's Disease

AD is the most common form of dementia, currently afflicting more than 5 million Americans. Health care costs related to AD have steadily risen and were estimated to be approximately $61 billion in 2002.[250] Currently, four genes have been strongly associated with the manifestation of AD. Early-onset AD usually is caused by an autosomal dominant mutation in any one of three genes—*PSEN1*, *PSEN2*, and *APP*—with symptoms of the disease developing before the age of 60. Most individuals, however, have the late-onset form of AD. To date, there is only one clearly established genetic risk factor for late-onset AD, the gene encoding apolipoprotein E (*ApoE*), the ε4 allele of which is associated with increased risk. The ε2 allele of *ApoE* is protective against the disease.

The patent landscape for AD is complex. Patents related to testing for all four genes have been issued in the United States, although the actual DNA sequences of the human *ApoE* and *APP* genes have not been patented (*APP* is the subject of several patents related to animal models of AD, however). There are five known patents related to the *PSEN1* and *PSEN2*, four of which are jointly assigned to the Hospital for Sick Children and the Governing Council of the University of Toronto and one that is assigned only to the Hospital for Sick Children. Athena Diagnostics has exclusive licenses to two of these patents, one of which covers the *PSEN2* gene and mutations, and the other covering a methods claim for *PSEN1*. A sixth patent covering a mutant *PSEN1* gene was assigned to the General Hospital Corporation in Boston; however, this patent was later abandoned and returned to the public domain.

[250] Alzheimer's Association. (2007). *Alzheimer's Disease Facts and Figures 2007*, http://www.alz.org/national/documents/Report_2007FactsAndFigures.pdf.

Duke University holds three "methods" patents on *ApoE* testing to predict the risk of the disease and has licensed them exclusively to Athena Diagnostics. According to Allen Roses, the first inventor on the *ApoE* patents, the patents were sought because of the extremely competitive nature of AD research in the early 1990s, and he wanted to establish documentation of his discovery. Dr. Roses indicated that the decision to exclusively license the *ApoE* patents to Athena Diagnostics was made to ensure that genotyping was conducted only on samples from individuals for whom a physician had a confirmed diagnosis of dementia rather than just presymptomatic screening for it. In March 2008, Athena Diagnostics sublicensed the patents to Smart Genetics, a direct-to-consumer genetic testing company that ultimately folded in October 2008. Graceful Earth, Inc., a health alternatives website, offers direct-to-consumer *ApoE* testing that does not require physician approval. Two alternative *ApoE* testing services are available in Canada. Finally, Navigenics, one of the new "personal genomics" direct-to-consumer companies, is providing information about AD risk based on an indirect assessment of *ApoE* genotype.

Due to a variety of factors including little ability to meaningfully intervene with the natural history of the disorder, broad screening for AD predisposition based on assessment of the associated genes is not recommended at this time . The three genes associated with early-onset AD do not account for all cases, and screening for them is considered appropriate only for descendants of individuals who had the disease. Testing for the *ApoE* gene is recommended only in an attempt to confirm diagnosis of individuals who already have developed dementia. Only about half of late-onset AD patients have an *ApoE* ε4 allele, and 15 to 25 percent of people with the allele do not develop the disease, even when they are at an advanced age.

It is difficult to determine whether patents have affected the cost of genetic testing for AD or limited access in other ways. Athena Diagnostics offers *ApoE* testing for $475. Smart Genetics, which held a sublicense for *ApoE* testing from Athena Diagnostics but ceased operations in October 2008, initially offered its services for $399, and later decreased its price to $249. Saint Louis University Health Science Center has offered

ApoE targeted mutation analysis for cardiovascular purposes, which does not violate Athena's patent rights, for $365. Two Canadian laboratories also offer *ApoE* testing for $100 (US) and $120 (CD).

Genetic testing for genes associated with early-onset AD are offered by Athena Diagnostics; however, testing services for *PSEN2* and *APP* have been publicly offered only since February 2008. The pricing structures for these tests are less transparent than those for *APOE*. Known prices are $1,675 for sequence analysis of the *PSEN1* gene, $2,750 for pre-implantation genetic diagnosis (PGD) analysis of *PSEN1*, and ~$5,000 for PGD analysis of the *APP* gene. Athena Diagnostics also offers sequence analysis of the *APP* and *PSEN2* genes, but list prices are not publicly available.

Coverage of genetic testing for AD-related genes varies among providers. A significant road block to coverage is the fact that AD is incurable, and thus the test results do not have a direct impact on treatment. Approximately one dozen insurers have policies regarding testing for genetic markers of familiar AD, but none of these policies formally and explicitly cover testing. Some health insurance companies deny claims based on the assertion that the tests are still experimental, while others will cover testing if a doctor deems it to be medically necessary.

The AD case study also provides an example of how patent rights can be used to ensure compliance with professional guidelines for genetic testing. Dr. Roses indicated that ensuring that *ApoE* genetic testing was used for patients already clinically diagnosed with dementia rather than as a presymptomatic screening test aligned it with existing clinical guidelines and was the main intent for pursuing an exclusive license with Athena Diagnostics, because testing activity could be better monitored with a single licensee. Athena enforced this provision by agreeing to test only if a physician stated the test was being conducted on someone with symptoms of dementia or in the context of research.

Similarly, in the case of Huntington disease, the owner of the patent, Massachusetts General Hospital, and the Hereditary Disease Foundation, which funded and helped

organize the scientific collaborations that resulted in the identification of the gene, also used patents to ensure that testing complied with professional guidelines.[251] Massachusetts General Hospital pursued this effort through a nonexclusive rather than an exclusive licensing strategy. The case studies presented in the appendices of this report found no evidence that compliance with professional guidelines requires exclusive licensing, although this strategy could simplify monitoring such compliance.

Cystic Fibrosis

The CF case study is a demonstration of how patents can be licensed in a manner that avoids many of the controversies associated with sole-source provider models, such as those for familial breast and ovarian cancer gene testing. The discovery of the CF transmembrane conductance regulator (*CFTR*) gene in 1989 by Drs. Lap-Chee Tsui and John Riordan of the Hospital for Sick Children in Toronto, and Francis Collins, then at the University of Michigan, was the culmination of nearly 40 years of research. The *CFTR* gene and the *Δ508* mutation that is the most common cause of CF (present in approximately 70 percent of all cases) were patented and nonexclusively licensed in order to promote the broad adoption and availability of genetic testing services. However, because CF is a relatively common disorder—affecting approximately 30,000 Americans—this strategy could not be broadly applied to genetic tests for more rare conditions. Currently, 63 laboratories in the United States offer testing for the *CFTR* gene. Because there is no cure for the disease, early detection and screening through genetic testing allows for improved disease management and counseling regarding reproductive options.

A survey of laboratories' prices for CF genetic testing, a review of the literature, and information about the cost-effectiveness of the CF test and the developing market for CF testing indicate that there is no evidence that the broadly licensed patents have significantly hindered access to genetic tests or the provision of cost-effective screening

[251] NRC, op. cit.

for CF. As previously mentioned, there are a large number of CF genetic test providers with test costs ranging from $1,200 to $2,762 for sequencing of the entire *CFTR* gene, to $84 to $595 for targeted mutation analysis that can evaluate from 1 mutation up to a panel of 100 mutations. DNA-based carrier and newborn screening for CF is available and endorsed by the American College of Medical Genetics (ACMG), the American College of Obstetricians and Gynecologists (ACOG), and NIH. ACMG and ACOG continue to update their guidelines based on data from test providers.

Current licensing practices appear to facilitate academic research as well as promote commercialization and the provision of testing products. The initial and annual licensing fees have remained unchanged since the initial license was granted in 1993. The initial license fee for the kit is $25,000, and $15,000 is charged for in-house commercial tests. Licensees of the test kit must agree to pay a 6 percent royalty on their net sales of products; however, this royalty rate is reduced should the licensee need to add technologies (e.g., mutations) to the final product—thus 3.6 percent royalty payments are generally agreed upon. Revenue from these fees and royalties has been applied toward covering the costs for worldwide patent protection of the *CFTR* gene sequence and mutations. The licensing strategies of the CF-related gene patents have been important for establishing platforms for newborn and population-based carrier screening that have become a standard of care.

An interesting component of the CF case study is the declaration of patent interference by USPTO regarding overlapping patents filed by two research groups (one group from the University of Michigan and Toronto's Hospital for Sick Children and the other from Genzyme Corporation), a feature unique to the U.S. intellectual property system. The current "first inventor to file" criterion for patent applications in the United States can lead to costly interference proceedings that are formal efforts by competitors to challenge a patent after it has been filed, potentially canceling a patent application by proving that the patent holder was not the first to invent. An interference proceeding against the claims of several CF patents filed by an investigator at the Hospital for Sick Children in collaboration with the University of Michigan took nearly a decade to resolve. The patent

reform initiative under consideration during the 110th Congress would have changed the U.S. system to the international "first-to-file" standard, most likely eliminating such situations. However, the cost and duration of the interference proceedings do not appear to have directly affected patient access to CF testing. An important point about this case was that the CF Foundation and researchers were included in the discussions and decision-making about the licensing of the patents. Through this process, they were able to ensure that the interests of patients were considered as the science progressed and the genetic testing evolved.

Hearing Loss

The hearing loss case study provides an opportunity to investigate whether the patenting of different genes by multiple parties has the ability to affect patient and clinical access to genetic testing. At least 65 genes have been implicated in genetic hearing loss, accounting for nearly half of all hearing loss cases. Mutations in just five genes—*GJB2*/*Connexin 26*, *GJB6/Connexin 30*, *SLC26A4/PDS*, *MTRNR1*, and *MTTS1*—are the most commonly tested for genes for hearing loss. Of these five genes, only two (*GJB2* and *MTRNR1*) are patented; these are exclusively licensed to Athena Diagnostics. Genetic testing for complex disorders such as hearing loss necessarily relies on the analysis of multiple genes or "multiplex tests"—a trend that will certainly increase. Thus, the patchwork of patented and unpatented genes for such disorders has raised several concerns, including the potential for "patent thickets" that might hinder the ability of providers to offer a genetic test if a license is not granted for a specific gene or mutation, if there is blocking of a comprehensive genetic test by a single patent owner, or if there is inflation of test costs because of royalty stacking.

Despite these concerns, the case study found no specific evidence of patents impeding the clinical adoption or utilization of genetic tests for hearing loss or that patents affected the availability of such tests. The majority of known hearing loss genes, including three of the five aforementioned most common genes, are not patented. There are multiple providers of genetic testing for hearing loss and an equally wide range of price points,

indicating that test price does not correlate with patent status. Direct test utilization data are sparse because of the decentralized availability of tests, but there is no evidence that patenting has affected, either positively or negatively, clinical or patient access in the United States. Moreover, patents appear to have had little to no impact on the dissemination of information about these tests or on how they are marketed.

Testing for *GJB2* mutations in the United States is licensed exclusively to Athena Diagnostics, but it also was offered by at least 10 other providers in 1999, a number of which were academic medical centers,[252] and this increased to 19 providers (18 nonprofit and 1 for-profit) in 2008.[253] The cost of Athena's *GJB2* full sequence analysis ($575) is nearly $100 more than the average price offered by the other providers, but it is in the middle of the price range of the full sequence analysis tests offered by universities, hospitals, and academic medical centers ($290 to $816). The per-amplicon price of the test offered by Athena Diagnostics is $287.50, which is comparable to the per-amplicon price of tests offered by nonprofit providers ($140.80 to $430). Athena Diagnostics also holds an exclusive license for *MTRNR1* testing, although the testing is also offered by six nonprofit providers. The price of Athena's *MTRNR1* test ($365) is higher than the price of testing offered by universities and hospitals ($150 to $285). It is unclear, however, whether Athena Diagnostics' higher price can be attributed to gene patents or other aspects of the testing service. Testing services for these two genes could be more complex if Athena Diagnostics chooses to enforce patents that could limit the number of providers offering testing.

There is no evidence that patents have had any impact, positive or negative, on research on the genetics of hearing loss. Research on both rare and common forms of hearing loss appears to have progressed independent of patent status. Microarray-based research and chip-based diagnostics for hearing loss are being performed by multiple groups. It is unclear how patents will affect development of and access to such chip- or microarray-

[252] Kenneson, A., Myers, M.F., Lubin, I.M., and C. Boyle. (2003). Genetic laboratory practices related to testing of the GJB2 (connexin 26) gene in the United States in 1999 and 2000. *Genetic Testing* 7(1):49-56.
[253] Information from http://genetests.org.

based diagnostics as that technology is developed, although this landscape could become more complex if Athena Diagnostics chooses to enforce its patent rights for the *GJB2* and *MTRNR1* genes, potentially resulting in patent thickets.

The authors of the hearing loss case study also noted that genetic testing for hearing loss takes place in a complex social context, and attitudes of individuals—both hearing and nonhearing—toward genetic testing may influence consumer utilization of tests.[254,255] This complicates the notion of "access," because individual values and preferences also affect the adoption and utilization of the tests. For those who deliberately choose not to use tests, lack of utilization does not necessarily indicate lack of access but rather an expression of choice. Statistics on utilization are always only a proxy for direct measures of access, but in the case of hearing loss, measuring access would require knowing not only the number of people who might benefit in clinical and technical terms, but also the number of those who would actually choose to seek the genetic test.

It is important to note that there has been intermittent enforcement for *GJB2* testing, although it is unclear how that has affected patient access to testing. Also note that testing landscape for *GJB2* may be quasi-stable. The discontinuation of Third Wave ASRs to test for the common mutation of *GJB2*(35delG) may change the numbers of providers who are able to test for this mutation without infringing patents licensed to Athena. This may be an emerging situation.

Hereditary Hemochromatosis

The case study on genetic testing for HH provides an example of how ownership of patent rights can introduce additional complexity and a level of uncertainty regarding the availability of a genetic test. HH is an iron metabolism disorder that leads to excess iron

[254]Burton, S., Withrow, K., Arnos, KS., Kalfoglou, A.L., and A. Pandya. (2006). A focus group study of consumer attitudes toward genetic testing and newborn screening for deafness. *Genetic Medicine* 8(12):779-783.
[255] Taneja, P.R., Pandya, A., Foley, D.L., Nicely, L.V., and K.S. Arnos. (2004). Attitudes of deaf individuals towards genetic testing. *American Journal of Medical Genetics* 130(1):17-21.

absorption, resulting in organ damage—particularly to the heart, liver, and pancreas. In extreme cases, HH can be fatal. It is an autosomal recessive disorder that results most often from a few specific mutations in the *HFE* gene,[256] which regulates iron absorption. HH is the most common recessive genetic disease[257] in some populations of Northern European descent, resulting in a relatively high carrier frequency.

The *HFE* gene, two mutations (*C282Y* and *H63D*), methods for detecting these mutations, and methods for analyzing these mutations using a kit were discovered and patented by Mercator Genetics, a start-up company, in the mid-1990s. This proved to be Mercator's singular scientific contribution before the company went out of business and was acquired by Progenitor in 1997. Rights to the *HFE* patents were sold to two successive companies, and these complex business transactions added uncertainty about how, when, and to what degree patent rights would be enforced. This uncertainty arguably affected the number of providers willing to offer the test, thus limiting access.

A 2002 article in the journal *Nature* concluded that testing for the *HFE* gene "failed the test" of socially optimal access.[258] According to the article, Progenitor exclusively licensed the patent rights to perform clinical testing of the HH mutations to SmithKline Beecham Clinical Laboratories (SBCL) for an up-front payment and guaranteed continuing fees valued at roughly $3 million.[259] This licensing agreement guaranteed SBCL's exclusive license and payments were due to Progenitor until a test kit was developed and available for use by clinical laboratories. SBCL began informing laboratories of their possible infringement activities in June 1998 and offered sublicenses

[256] Schmitt, B., et al. (2005). Screening primary care patients for hereditary hemochromatosis with transferrin saturation and serum ferritim level: systematic review for the American College of Physicians. *Annals of Internal Medicine* 143:522-536.

[257] The reason for higher population frequency in Northern Europe is not known. One intriguing, but still speculative, theory posits a survival advantage among those with HH mutations in resisting infections, causing plague and other diseases prevalent in Europe. See, for example, Moalen, S., et al. (2004). Hemochromatosis and the enigma of misplaced iron: Implications for infectious disease and survival. *Biometals* 17(2):135-139. Another hypothesis, which is not incompatible, is co-selection of hemochromatosis and certain major histocompatibility loci involved in immune function. See, for example, Cardozo, C.S., et al. (2002). Co-selection of the *C64D* mutation and *HLA-A29* allele: A new paradigm of linkage disequilibrium? *Immunogenetics* 53:1002-1008.

[258] Merz, J.F., Kriss, A., et al. (2002). Diagnostic testing fails the test. *Nature* 415(6872):577-579.

[259] Ibid.

to academic laboratories for a $25,000 up-front fee. The fee for commercial laboratories ranged from 5 to 10 times this amount. SBCL also reportedly demanded royalties as high as $20 per test.[260] SBCL and its rights for HH clinical testing were sold to Quest Diagnostics in 1999.

BioRad Ltd. purchased most of the patents relating to HH genetic testing and the *HFE* gene from Progenitor in 1999. This acquisition was subject to the exclusive license held by SBCL. In 2000, Quest Diagnostics transferred this license to BioRad Ltd., terms of which were undisclosed. BioRad continued to expand its HH patent portfolio and acquired additional patents related to *HFE* gene products. In 2001, it began offering analyte-specific reagents for the testing of two *HFE* alleles, *C282Y* and *H63D*. BioRad currently offers two test kits for HH, the purchase price of which ($2,016 for 24 tests; $84 per test) includes a sublicense from the company to perform the test. The sublicensing fees for laboratories opting to offer in-house-developed tests rather than the BioRad kits are unknown.

A 1998 survey indicated that 58 laboratories were performing *HFE* testing at that time, prior to the issue of the Mercator *HFE* patents.[261] Upon acquisition of its exclusive license rights from Progenitor, SBCL began issuing letters to laboratories offering HH testing to make them aware of its intellectual property rights and to offer a sublicense. In the aforementioned survey, only four of 58 labs offering HH testing (of 119 that were surveyed) stopped offering it, and, of those four, only two stated that patents were the reason they decided to stop offering the test.[262] As of May 2007, 37 laboratories were listed on the Genetests.org website as providers of *HFE* testing. In addition, the test is offered directly to consumers by DNA Direct and Health-Test Direct.

Although the test did not become a universal screening test as initially envisioned by Mercator scientists, testing is relatively easy to obtain, both through physicians and

[260] Ibid.
[261] Cho, M.K. *Effects of Gene Patents and Licenses on Clinical Genetic Testing*. Presentation to SACGHS. June 27, 2006, http://oba.od.nih.gov/oba/SACGHS/meetings/June2006/Cho.pdf [accessed January 9, 2008].
[262] Ibid.

through direct-to-consumer services. Prices for the targeted testing of the *C282Y* and *H63D* alleles vary based on the platform technology utilized (targeted mutation analysis, allele-specific analysis, RFLP/electrophoresis analysis). Looking at a subset of providers, it appears that test costs can range from $158 to $467.25. DNA Direct, a direct-to-consumer genetic testing service, offers *HFE* genetic testing for $199.

In summary, the *HFE* patent story shows how patents can introduce transaction costs and uncertainty, but it also shows that patenting need not hinder access in the long run. In this case, a judgment about the value of patenting may center on views regarding (1) the fair disposition of rewards for winning a "discovery" race by a few months and (2) the value of having patent incentives for small biotechnology start-ups as part of the innovation ecosystem. The patents seem to have been neither necessary for discovery of the gene and development of a genetic test nor a permanent hindrance to broad access.

A key point in this case study is that a change in the clinical use of the test as the science improved, that is, the decision that genetic testing was no longer recommended for population screening, may have influenced how the intellectual property was managed, shifting focus from exclusive licensing to non-exclusive licensing for ASRs. In addition, the practices and business models of the different owners of these patents influenced how it was licensed, creating temporary turbulence.

Spinocerebellar Ataxia

SCA is a designation given to a rare subset of heritable progressive neurological diseases characterized by loss of cells in the cerebellar portion of the brain. Symptoms include ataxia, or irregular uncontrolled movement, and often symptoms that are attributable to the loss of brainstem and spinal cord function.[263, 264] Although ataxia is a common symptom found in conditions ranging from chronic alcoholism to stroke, SCA accounts

[263] Schols, L., Bauer, P., Schmidt, T., Schulte, T., Riess, O. (2004). Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. *Lancet Neurology* 3(5):291-304.
[264] Taroni, F., and S. DiDonato. (2004). Pathways to motor incoordination: the inherited ataxias. *National Review of Neuroscience* 5(8):641-655.

for less than 5 percent of the ataxic population.[265] There are currently more than 30 identified variants of SCA. Therefore, the disease is highly genetically heterogeneous, with dozens of genes responsible for conditions that are clinically similar, adding to the complexity of diagnosis. The case study on genetic testing for SCA focuses on the six most common forms, SCA 1-3 and SCA 6-8.

Genetic tests are currently available for 15 variants of SCA. Athena Diagnostics holds the patent or has an exclusive license rights for 12 patents that identify the most commonly occurring variants (SCA 1-3 and SCA 6-8), accounting for roughly 60 to 80 percent of known SCA cases, depending on the patient's country of origin.[266] Of these 12 patents, 6 are licensed from the University of Minnesota, and 3 others are licensed from other academic institutions or their affiliated research foundations. Only one of these patents arose from in-house R&D at Athena. In addition, Athena was granted a nonexclusive license by Baylor Medical College for a patent that covers methods for detecting SCA-10.[267]

Athena has enforced its exclusive licenses and is widely assumed to be the sole distributor of these tests.[268] Its legal department has sent cease and desist letters to some laboratories performing licensed SCA genetic tests. After receiving such a letter, the

[265] Mori, M., Adachi, Y., Kusumi, M., and K. Nakashima. (2001). A genetic epidemiological study of spinocerebellar ataxias in Tottori prefecture, Japan. *Neuroepidemiology* 20(2):144-149; Moseley, M.L., Benzow, K.A., Schut, L.J., Bird, T.D., Gomez, C.M., et al. (1998). Incidence of dominant spinocerebellar and Friedreich triplet repeats among 361 ataxia families. *Neurology* 51(6):1666-1671; van de Warrenburg, B.P., Sinke, R.J., Verschuuren-Bemelmans, C.C., Scheffer, H., Brunt, E.R., et al. (2002). Spinocerebellar ataxias in the Netherlands: prevalence and age at onset variance analysis. *Neurology* 58(5):702-708.

[266] Bauer, P.O., Zumrova, A., Matoska, V., Marikova, T., Krilova, S., et al. (2005). Absence of spinocerebellar ataxia type 3/Machado-Joseph disease within ataxic patients in the Czech population. *European Journal of Neurology* 12(11):851-857; Lee, W.Y., Jin, D.K., Oh, M.R., Lee, J.E., Song, S.M., et al. (2003). Frequency analysis and clinical characterization of spinocerebellar ataxia types 1, 2, 3, 6, and 7 in Korean patients. *Archives of Neurology* 60(6):858-863; Tang, B., Liu, C., Shen, L., Dai, H., Pan, Q., et al. (2000). Frequency of SCA1, SCA2, SCA3/MJD, SCA6, SCA7, and DRPLA CAG trinucleotide repeat expansion in patients with hereditary spinocerebellar ataxia from Chinese kindreds. *Archives of Neurology* 57(4):540-544.

[267] E-mail and phone correspondence with Teresa L. Rakow, Sr. Licensing Associate, Baylor Licensing Group, Baylor College of Medicine, April 9, 2008.

[268] Cho, M., Illangasekare, S., Weaver, M.A., Leonard, D.G., and J.F. Merz. (2003). Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnostics* 5(1):3-8; Schissel, A., Merz, J.F., and M. Cho. (1999). Survey confirms fears about licensing of genetic tests. *Nature* 402(6758):118.

Diagnostic Molecular Pathology Laboratory at the University of California, Los Angeles stopped offering SCA testing. According to Dr. Wayne Grody,[269] director of the laboratory, the terms of the sublicense offered by Athena Diagnostics were "unreasonable and not economically viable." It is interesting to note, however, that Athena Diagnostics does not list prenatal or preimplantation genetic diagnosis as part of its SCA testing services, and apparently does not enforce its patents against such testing, although several laboratories are listed as offering such services on the genetests.org website.[270]

SCA genetic tests can be performed individually for as little as $400 or for as much as $2,335, depending on whether the test is for specific known mutations or for full-gene sequencing, respectively. Athena Diagnostics also offers the Complete Ataxia Panel, a compilation of 13 tests that covers the most commonly identified SCA mutations, for $7,300. From a clinical standpoint, this often is the best option, given the genetic heterogeneity inherent in these clinically similar disorders.

Athena Diagnostics' collection of SCA patents and licenses enables a single laboratory to test for many disease variants and helps to protect the company's investment in certification under the Clinical Laboratory Improvement Amendments (CLIA) program,[271] its ability to conduct laboratory proficiency testing, its ability to hire a sales force dedicated to educating neurologists about the tests, and its ability to fulfill the staffing needs required to manage the complex coverage and reimbursement policies. The syndromes are relatively rare, and this full range of tests might not be available without the patent incentive. The counter argument is that Athena Diagnostics has assembled an effective monopoly on SCA genetic testing. It has been aggressive in enforcing its patent rights, leading several laboratories to stop offering testing for SCA, thus limiting

[269] Phone conversation with Dr. Wayne Grody, March 21, 2008.
[270] Several laboratories on the website www.genetests.org are listed as performing these tests. The authors of the case studies did not verify or pursue questions regarding these test offerings.
[271] The CLIA program sets standards and issues certificates for clinical laboratory testing. CLIA defines a clinical laboratory as any facility that performs laboratory testing on specimens derived from humans for the purpose of providing information (1) for the diagnosis, prevention, or treatment of disease or impairment, and (2) for the assessment of health. See http://wwwn.cdc.gov/clia/default.aspx,

alternatives for verification of test results and reducing the incentive to introduce cheaper and faster tests, because the current technology is protected by patents.

Three neurologists interviewed for the case study said they prescribed SCA genetic testing based on best medical practice, not price. Despite their belief that Athena Diagnostics' prices are higher than what their home institutions' laboratories might charge, they did not believe that lowering the price of testing to $100 would increase the number of tests they ordered. Of 16 Ataxia patients contacted through the National Ataxia Foundation website, a majority considered genetic testing accessible, even with costs up to $7,300. Three patients, however, said the tests were not covered by their health insurance and that they could not afford to pay for the test out of pocket. Athena Diagnostics offers a formal Patient Protection Plan that limits patients' out-of-pocket expenditures to 20 percent of the test fee—the usual copayment for most insurance programs. It also offers an additional plan for low-income families who find the 20 percent copayment prohibitive. Few data exist to indicate how well this option works in practice.

In summary, the SCA case study provides an example of genetic testing for a relatively rare and complex range of neurological disorders for which the intellectual property rights to the most common variants have been aggregated by a commercial laboratory that serves as the sole provider of testing services. There has been some concern that the aggressive enforcement of these patent rights has led several laboratories to cease existing testing services or to not consider offering them at all, potentially limiting access. Supporters of intellectual property consolidation argue that patent protection was required in order to sustain testing services for such a rare disorder.

Canavan and Tay-Sachs Diseases

Canavan disease and Tay-Sachs disease are devastating neurological conditions that predominantly affect the Ashkenazi Jewish population. Each is caused by inheriting two mutated copies (one from each parent) of a particular gene—hexosaminidase A (*HexA*)

for Tay-Sachs and aspartoacylase (*ASPA*) for Canavan disease. DNA-based carrier screening is available for Canavan and Tay-Sachs diseases, and an enzyme assay is also available for Tay-Sachs screening. The *HexA* (Tay-Sachs) and *ASPA* (Canavan) genes are both patented; however, the *HexA* patent was never commercialized, licensed, or enforced. The *ASPA* patent has been licensed at least 20 times.

The enzyme test for Tay-Sachs was developed in the 1970s and was used to spearhead very successful Tay-Sachs carrier screening campaigns in more than 100 U.S. cities, reducing the incidence of the disease by more than 90 percent. The enzymatic test is highly effective, detecting 97 to 98 percent of carriers, and has never been patented. In the late 1980s, a researcher at NIH identified the DNA sequence of the defective Tay-Sachs gene and developed a DNA-based diagnostic method. Both of these discoveries were patented by NIH but were never licensed or enforced.

The DNA sequence of the *ASPA* gene and a common mutation that resulted in Canavan disease were identified and published on October 1, 1993, by a scientist affiliated with Miami Children's Hospital (MCH). This discovery was very important, because it provided the tools for the development of a DNA-based Canavan screening test following several unsuccessful attempts to develop a clinically useful enzymatic test similar to the test for Tay-Sachs. The scientist's research had been heavily supported by Daniel and Deborah Greenberg of Chicago, parents of two children born with Canavan disease, and by various Canavan disease groups. MCH filed a patent application on September 29, 1993, and patents covering the DNA sequence and methods of screening for mutations were issued in October 1997, and MCH began vigorously enforcing its patent rights.

In a series of letters to laboratories and hospitals, MCH threatened infringement suits against test providers who did not take out licenses, demanded royalties for each test administered (initially set at $25 per test and later marked down to $12.50 per test), and established a test volume limit of 100 for individual laboratories. After failing to persuade MCH to soften the restrictions in its marketing plan, Daniel Greenberg and Canavan support groups sued the hospital in October 2000, charging breach of fiduciary duty,

unjust enrichment, and other offenses. The suit was settled out of court in August 2003. The settlement permitted MCH to license and collect royalties for Canavan disease gene testing—although the agreed-upon royalty rate has not been disclosed—and provided for license-free use of the gene in research. Today, there is no significant pricing difference between DNA tests for Canavan and Tay-Sachs. Full sequence analysis for the Tay-Sachs gene averages ~$1,536 compared to ~$1,198 for Canavan. Targeted mutation analysis averages to ~$292 for Tay-Sachs versus ~$298 for Canavan. The more common enzyme assay for Tay-Sachs has an average price of $204.

Patented genes for many other rare disorders have not generated such controversy, and the initial licensing contracts proposed by MCH appear to have been the immediate cause of conflict, rather than the existence of patents *per se*. Key mistakes include inattention to key constituencies, overpricing of a test mainly used for screening,[272] and attempts to impose quotas on laboratories that disrupted existing screening and testing programs in the target populations. Had MCH's initial licensing terms held, intellectual property rights might have resulted in reduced patient and clinical access to genetic screening for Canavan disease. The legal actions that the Canavan community pursued may have played a role in mitigating any long-term access problems that might have resulted.

In the end, access to and costs of genetic testing for Canavan disease and Tay-Sachs disease appear to be similar, despite the very different historical pathways and degrees of public controversy. In 2007, Genetests.org listed 37 facilities providing Canavan disease testing, disease diagnosis, and/or carrier screening and 34 laboratories offering Tay-Sachs disease testing. Of these, 26 offer testing services for both diseases.

[272] One basis for the criticisms of pricing is the initial $25 fee (with one report of an initial $50 fee), later reduced to $12.50 per test, and presumably changed in the settlement agreement. This is well within range for genetic diagnostics, but is unworkable for prenatal and carrier screening. By way of comparison, no state paid more than $60, and some states paid as little as $14.50, for their battery of newborn screening tests in late 2002, including all test-associated costs (not just royalty for a single component test, and including from 3 to 33 conditions). See U.S. General Accounting Office. (2003). *Newborn Screening: Characteristics of State Programs*. Washington D.C.: U.S. General Accounting Office.

Long QT Syndrome

Controversies surrounding the enforcement of intellectual property rights in genetic testing for familial LQTS were the subject of congressional testimony during a 2007 hearing on the role of gene patents in research and genetic testing,[273] prompting SACGHS to commission a case study that examined the patent and licensing landscape for genetic testing of LQTS. Unlike some of the disorders examined in the other case studies, LQTS is a relatively common Mendelian disorder. It is an interesting subject for a case study, because it is an example of a disease that can result from multiple mutations in multiple genes, for which commercial testing for a portion of these genes (but not all) is currently offered through a sole provider. In addition, a potential competitor has been acquiring intellectual property rights for LQTS genes and mutations for which commercial testing is not available, potentially setting up a situation of mutual blocking, unless cross-licensing or other agreements are reached. The LQTS case study presents a second example of an exclusive licensee for the genes of a major disease (*BRCA1* and *BRCA2* testing is the other example presented as part of this report). This case study also presents an example in which a patented genetic test initially was offered without patent enforcement, followed by a period during which patent rights were strongly enforced, thus providing some insights regarding the pre- and post-enforcement environments, although limited and with significant caveats.

LQTS is a condition in which patients' hearts fail to correctly "recharge" after heartbeats, and it can lead to life-threatening arrhythmias. LQTS affects 1 in 3,000 newborns and accounts for a small but significant fraction of sudden death in young people.[274] Mutations in 12 susceptibility genes account for approximately 75 percent of familial LQTS, with mutations in three genes, *KCNQ1* (*LQT1*), *KCNH2* (*LQT2*), and *SCN5A* (*LQT3*) accounting for most (70 percent) cases. Genetic testing is important for LQTS,

[273] *Stifling or Stimulating: The Role of Gene Patents in Research and Genetic Testing.* Hearing of Subcommittee on Courts, the Internet, and Intellectual Property of the U.S. House of Representatives Committee of the Judiciary. October 30, 2007. Washington, D.C. Hearing materials available at http://judiciary.house.gov/hearings/hear_103007.html.

[274] Goldenberg, I., and A.J. Moss. (2008). Long QT syndrome. *Journal of the American College of Cardiology* 51(24):2291-300.

because knowing which gene mutation an individual has can have a direct bearing on decisions regarding preventive measures and therapies.[275, 276]

The susceptibility genes accounting for the majority of LQTS cases were discovered by a researcher at the University of Utah in the mid-1990s, whose work was partially funded by NIH. The first LQTS gene patent was awarded in 1997. Unlike some of the other case studies conducted for the SACGHS report, the prospect of patents did not appear to be a primary incentive for the discovery of genes related to LQTS, most likely because of the relative rarity and heterogeneity of the disorder and the presumed small market for genetic testing. The University of Utah Research Foundation exclusively licensed its three patents covering the major genes predisposing to *LQT1*, *LQT2*, *LQT3*, and *LQT5* to DNA Sciences Inc., from 1999 to 2003.[277] In 2003, the assets of DNA Sciences were purchased by Genaissance Pharmaceuticals through a bankruptcy settlement.[278] Genaissance Pharmaceuticals launched commercial LQTS testing in 2004 under the name FAMILION®, and in 2005, Genaissance was acquired by Clinical Data, Inc. PGxHealth™, a subsidiary of Clinical Data Inc., has since overseen the rapid growth in commercial testing for LQTS and related disorders. The company has also launched a provider-focused sales force to help drive utilization and adoption of the FAMILION® test by physicians who treat individuals diagnosed with or suspected to suffer from LQTS.

Prior to the launch of the FAMILION® test for full-sequence analysis of five LQTS genes, there were at least two other fee-for-service providers of genetic testing for LQTS that screened approximately one-third of the five genes' combined coding sequence. The companies estimated this assay could be used to detect 87 percent of the mutations in five

[275] Tan, H.L., et al. (2006). Genotype-specific onset of arrhythmias in congenital long-QT syndrome: possible therapy implications. *Circulation* 114(20):2096-2103.
[276] Ackerman, M.J., (2005). Genotype-phenotype relationships in congenital long-QT syndrome. *Journal of Electrocardiology* 38(4 Suppl):64-68.
[277] Rienhoff, H.Y. (2008). Interview with Hugh Y. Rienhoff, Jr., M.D., founder and former CEO of DNA Sciences Inc. June 13, 2008.
[278] Company News–DNA Sciences declares bankruptcy, sells assets to Genaissance Pharmaceuticals. (2003). *Biotechnology Law Report* 22(3):307.

genes with a 59-percent sensitivity.[279] At that time, there was an assumption that LQTS would resemble CF, because one or a few major mutations would account for most of the disease burden, in addition to rarer mutations.[280] The assays conducted by these laboratories were similar but not identical in terms of sequence analysis, and both laboratories offered prenatal testing. The assay that screened 17 amplicons across the *LQT1*, *LQT2*, *LQT3*, *LQT5*, and *LQT6* susceptibility genes cost $2,200 in 2002 (~$129 per amplicon). Confirmation of a mutation in a family member cost $350.

Enforcement actions of DNA Sciences, Inc., regarding the LQTS intellectual property rights prompted one of these providers to cease testing in 2002. Genaissance did not launch its FAMILION® test until May 2004, and thus it is likely that there was a period of approximately 18 months in which genetic testing for LQTS was limited to academic laboratories. Since 2005, the rights to the *LQT1*, *LQT2*, *LQT3*, *LQT5*, and *LQT6* susceptibility genes have been exclusively licensed to Clinical Data and its subsidiary, PGxHealth, and the company has not sublicensed its test to any other diagnostic testing firms in the United States.

PGxHealth has been criticized for the high cost of FAMILION® LQTS testing. The test costs $5,400 per patient and $900 per confirmatory test in family members. This breaks down to approximately $74 per amplicon, nearly twice as much as the per-amplicon cost of hereditary breast cancer testing ($38), another test offered by a sole provider, but less than the $129 per-amplicon cost of one of the LQTS testing services offered prior to patent enforcement. Based on information presented in the case study, there were concerns among patients and physicians regarding the cost of the FAMILION® test as well as the incomplete or lack of coverage by most payers. Currently, FAMILION® testing is wholly or partially covered by 28 health plans, including TRICARE, and by Medicaid in 38 states (the company has applied for Medicaid coverage in all 50 states and other jurisdictions). Coverage of the test increased dramatically in 2007-2008.

[279] Refer to Appendix 8 of the case study, "Intellectual Property and Its Impact on Genetic Testing for Long QT Syndrome," which appears in the appendices of this report.
[280] Tsui, L.C., and P. Durie. (1997). Genotype and phenotype in cystic fibrosis. *Hospital Practice (Minneap)* 32(6):115-118, 23-9, 34, passim.

Opponents of the sole provider status of PGxHealth argue that multiple test providers also would serve to drive down testing costs and promote favorable coverage decisions.

PGxHealth also has been criticized for occasional errors, such as missed mutations or misinterpretation of results, and other issues related to experimentation and limited external verification of results. One investigator has expressed concern about the difficulty PGxHealth has performing reliable FAMILION® testing on paraffin-embedded samples from deceased patients, although this is a service rarely if ever offered in any clinical genetic testing context. PGxHealth does not offer prenatal testing for the disorder, which had been offered by the fee-for-service testing providers prior to patent enforcement in 2002.

There also have been concerns regarding test quality and the reproducibility of results. FAMILION® testing is conducted in a CLIA-certified laboratory, and PGxHealth conducts internal biannual proficiency testing.[281] Several clinicians have expressed concerns about the lack of regular external verification and interpretation of test results, particularly for a disorder in which precise diagnosis may be paramount for determining treatment and lifestyle options. The quality of the FAMILION® test also was questioned because of the discovery of allelic dropout problems shortly after the test was launched. This is a phenomenon related to DNA amplification in which some mutations are not detected even when present, thus resulting in a false-negative test result. The company presented its experiences with this problem and published a research paper on the discovery and avoidance of allelic dropout[282] that ultimately improved the sensitivity of the test.

Finally, PGxHealth has been criticized for its unwillingness to add genes to the FAMILION® test panel or share its clinical data with other researchers through scientific

[281] Reed, C., and Salisbury, B. (2008). Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth. June 12.
[282] Tester, D.J., Cronk, L.B., Carr, J.L., Schuz, V., Salisbury, B.A., Judson, R.S., Ackerman, M.J. (2006). Allelic drop-out in long QT syndrome genetic testing: a possible mechanism underlying false negative results. *Heart Rhythm* 3(7):815-821.

publications or access to databases. According to PGxHealth, additional genes have not been added to the FAMILION® test panel because of the rarity of the mutations in the seven other genes and because mutations are not as well characterized as those already tested. Patients who are not found to have a mutation in the five genes included in the FAMILION® test panel are referred to a research laboratory for additional screening. Currently, a patient is unable to receive testing for all 12 LQTS genes in 1 test, possibly resulting in delays in diagnosis and treatment. It is interesting to note that a potential competitor of PGxHealth, Bio-Reference Laboratories, has acquired exclusive licenses (also from the University of Utah) for 13 patents related to composition of matter and/or mutation detection in *LQT1*, *LQT2*, *LQT3*, *LQT5*, *LQT6*, and *LQT7*, resulting in fragmentation of the intellectual property rights related to LQTS that could result in a mutual blocking situation.[283] As of early 2009, this situation was continuing to unfold.

Through 2008, Clinical Data had not shared information on its mutations through a corporate equivalent of a LQTS mutation database, unlike the contributions Myriad Genetics made to public *BRCA* mutations databases. In November 2008, Clinical Data announced that its LQTS mutation data would be made public in spring 2009.[284] Prior to this announcement, there were two known databases of LQTS patients, typically containing data from research laboratories rather than FAMILION® testing. It is hoped that the sharing of such clinical and phenotypic information among researchers and clinical test providers (both current and potential) will help further the knowledge base of the complex genetics associated with LQTS.

The case study on LQTS highlights several areas of concern regarding sole-source providers, particularly regarding a disorder for which the understanding of the genetics involved is incomplete. In addition to disagreements involving test cost and quality of services offered, there is no consensus regarding whether understanding of the disorder and its associated mutations and variants would progress more rapidly if there were

[283] See Appendix 6 of the attached case study.
[284] Clinical Data launches genetic test for arrhythmogenic right ventricular cardiomyopathy (AVRC); Company to release its genetic databases for inherited cardiac conditions. *Business Wire.* November 10, 2008.

2549 additional commercial laboratories conducting testing and acquiring data on and
2550 characterizing new mutations.
2551

Chapter IV

Key Findings and Preliminary Conclusions

Based on its review of the literature, case studies, and review of international policies regarding gene patents, SACGHS found little in the way of broad or consistent evidence that indicates either positive or negative effects of gene patents on patient access to diagnostic tests. Evidence exists about the impact of other factors, such as oversight and regulation of genetic tests and coverage and reimbursement policies, on patient and clinical access to genetic tests, and SACGHS has extensively addressed these issues in previous reports.[285] Although it is difficult to document measurable and systematic impacts, either positive or negative, of gene patents on patient access to tests, SACGHS did identify several issues of concern that, if not addressed, might result in future barriers to patient access as the number and complexity of gene tests increases. Finally, in the case of patents, perceptions can have important impacts on behavior and can affect the willingness of researchers to investigate a particular problem, the willingness of companies to operate in a particular region, the willingness of academic laboratories to develop a given test, and the actions of clinicians who order and utilize genetic tests.

Key Findings from the Case Studies

SACGHS identified key findings for the following six issues:

- whether the prospect of a patent encouraged researchers to search for gene-disease associations that could be developed into a genetic test;
- the role patents play in the development or commercialization[286] of a genetic test based on a discovered gene-disease association;
- the effect of patent(s) and licensing practices on the price of a genetic test;
- the effect of patent(s) and licensing practices on the availability of a genetic test;

[285] See *Coverage and Reimbursement of Genetic Tests and Services* and *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*.
[286] As used in the questions, commercialization means "to offer for sale; make available as a commodity."

- how patent(s) on a genetic test and the related licensing practices affected the ability of others to innovate on the test; and
- the prospect that a patent or licensing practice may cause a particular harm to genetic testing in the future.

The overall findings from the case studies and their import are discussed below.

Did the prospect of a patent encourage researchers to search for gene-disease associations that could be developed into a genetic test?

In general, the prospect of receiving a patent was not the major force motivating scientists to search for gene-disease associations that could be used to develop a genetic test. However, it also appears that the prospect of a patent for a therapeutic attracted investment into Myriad Genetics that was then used to carry out continued genetics research into breast cancer; similarly, the prospect of patents attracted investment into Mercator Genetics, which used the money to conduct genetics research and eventually found the HH gene. These investments were particularly critical as they helped Mercator and Myriad win "races" (by a few months) to identify the relevant mutations. In the search for colon cancer genes, Johns Hopkins University partnered with a company, which presumably was motivated by patents to aid Hopkins's search.

Based on the above, it seems to reasonable to conclude that if patent protection for genetic tests did not exist, scientists likely would continue to pursue research into gene-disease associations with equal fervor, motivated by various factors, including the desire to advance the understanding of a disease, earn the esteem of their colleagues and advance their individual careers. Whether companies would continue to pursue this research if patents did not exist is unclear and would be a difficult hypothesis to test.

What role did patents play in the commercialization of the genetic tests?

The case studies suggest that for those who secured a patent on a gene-disease association, there was an incentive to commercially develop a genetic test. Patents also can be consolidated by one company that can then offer testing for all the alleles protected by those patents. At the same time, the case studies found that a patent is not a necessary step for commercialization; genetic tests are widely available in the absence of a patent on a gene-disease association. For example, in the hearing loss case study, both nonprofit and for-profit providers developed genetic tests on unpatented genes. Similarly, laboratories developed genetic tests for HH based on published research findings; a patent incentive was not needed. Although the case studies do not shed much light on how much capital and investment is needed to commercialize a genetic test, they do suggest that development costs for diagnostics are sufficiently low that most academic medical centers have had adequate resources to develop a test even in the absence of a patent, at least to the point of establishing its analytical validity and understanding its clinical validity in certain populations.

Therefore, a patent apparently is not uniformly a necessary incentive to develop or commercialize a genetic test. Patents, however, may be necessary to stimulate commercial development of genetic tests for rare alleles. Clinical Laboratory Improvement Amendments-approved tests for such alleles often are unavailable; in some cases, research laboratories offer this testing, but not always.

For conditions that involve multiple genes (the usual situation in human genetics), a subset of which are the most common cause of the disease, the holder of those patents can become a dominant provider, because the market for testing the rarer genes is so limited. The discoverers of the rarer genes, seeing that the more common genes have been patented and used to develop a test, can conclude that it is not economically viable to develop the rarer genes into commercial tests because the demand for such tests would

likely be limited to the portion of patients who do possess the rare mutations.[287] Discoverers of the rarer genes generally have two options—allow broad access to their discoveries or patent them and license to the holder of the dominant patents. In either case, the holder of patents on the most common genes gains access to the rarer genes. In the latter case, however, the cost of a license would likely affect the price of the test for the patient. Dominant patent holders, because they have access to more data, are also in a better position to discover new mutations, further strengthening their control of the market.

In the case of genetic testing for Long QT syndrome (LQTS), two different commercial testing laboratories have acquired rights to different genes and mutations. According to the case study, a mutual blocking situation may be developing—neither testing service has rights to test for the full range of mutations and clinicians who wish to obtain testing for a patient cannot know in advance which test to choose. The impact of these developments on LQTS genetic testing, particularly with respect to pricing and insurer coverage and the prospect of litigation, cross-licensing, or other negotiated legal agreement, is unclear and concerning at the time of this writing.

More information is needed on how unpatented genetic tests compare with patented genetic tests in terms of quality and efficiency. Do patent holders operate in a more effective way, reaching more patients and providing better service? Do companies as well as nonprofit medical centers regularly develop genetic tests from unpatented genes as would seem the case for many conditions? More data would further inform the question of whether patents generally are needed for a test developer to offer high-quality testing service. However, it is difficult to compare the quality of patented and unpatented genetic tests without independent proficiency testing.

[287] These tests may be available on a research-only basis, if available at all.

How did patents and licensing practices affect price?

The case studies attempted to evaluate how patents and licensing practices affected the price of genetic tests, but could not always reach definite conclusions because of difficulties in obtaining relevant data and challenges in determining the relative contribution of various factors, including overhead costs, to price. For two of the case studies (Alzheimer's disease and LQTS), some findings suggest that the price of the patent-protected test was higher than it would have been had the test been unpatented, with the potential that this price is reducing patient utilization of the test. In addition, it appears that the test developers of the Canavan disease genetic test used their patent monopoly to establish restrictive license conditions and sought fees that exceeded what laboratories offering similar tests for Tay-Sachs disease were willing to pay. Angered by these terms, a consortium organized against the patent holder, initiated a lawsuit roughly a year after the license terms were first proposed, and negotiated a settlement that altered the license terms in a way that the plaintiffs apparently considered acceptable. One surprising finding from the case studies was that the per-unit price of the full-sequence *BRCA* test, which often is cited as being priced very high, was actually quite comparable to the price of other full-sequence tests done by polymerase chain reaction (PCR), at both nonprofit and for-profit testing laboratories.

Thus, there is at least the risk that a patent-protected genetic test will have an inflated price; this inflated price, in turn, may reduce how many patients use the test. Licensing many providers may mitigate price inflation. However, various factors other than patenting and licensing affect the price of genetic tests, including ordinary market forces, such as demand and market size (where there is a large market and high demand, the company stands to make considerable revenue even at a lower price). Many of these factors exert a downward pressure on price. For instance, health insurance providers often will not cover a test that is priced too high, so companies choose to keep the price low so that the test will be covered, which in turn makes the test more affordable to patients. Similarly, a company also has an incentive to set its price in the price range of other genetic tests covered by Medicare, Medicaid, and other private payers (by a formula for

number of PCR amplicons being sequenced, for example) to reduce payer resistance to covering the new test. Competition from related tests that do not infringe the patent and foreign competition also operate to lower the price of genetic tests. Thus, multiple factors constrain patent holders and exclusive licensees from using their monopoly power to set prices at will.

It remains to be seen whether the price of genetic tests will drop when the patents expire. When a patent on a therapeutic agent expires, competition from generics that enter the market generally results in a significant price drop. In diagnostics, on the other hand, multiple factors already constrain the price a sole provider of a genetic test may set. It is also unclear whether competition from new test providers after patent expiration will reduce prices.

How did patents and licensing practices affect availability?

The case studies generally found that for patented tests that were licensed to many providers, there was no evidence of any limitations on availability. Where there is a sole provider, due to the patent holder practicing the patent exclusively or licensing exclusively to a single entity, the effects on availability can be positive or negative. Although a sole provider has an incentive to reach as many patients as possible (making the test widely available) and to ensure payment from as many payers as possible, the sole provider's particular business decisions or practices could frustrate that goal. For example, the test provider may not advertise sufficiently to health care providers (with the result that clinicians cannot inform their patients of the test), or the provider may not include less common gene variants in its testing. In this case, although a test would still be available, the ideal test for a particular patient would not be available. If the provider had to compete against equivalent tests, any problems in test quality and availability might be remedied.

Sole providers also could seek to inflate the market by testing patients when testing is not indicated. This could be true of any provider, but the incentive may be stronger for single

providers with patent protection. Although sole providers have an incentive to secure broad insurance coverage for their tests, they sometimes can fail to secure coverage contracts with certain payers. As a result, patients covered by those insurers may not have access to testing because they cannot afford to pay the full costs of the genetic test out-of-pocket. For example, in the hearing loss case study, because Athena does not have a contract with MediCal, the California Medicaid program, indigent patients have had difficulty obtaining Athena's patented test, and no alternative test is available. A similar situation exists with regard to testing for SCA according to clinicians in California. Competition would mitigate this type of problem, if not eliminate it altogether: Companies offering a test would compete for contracts with payers, increasing the likelihood that a patient could find at least one test provider that had a contract with the patient's health insurance provider. A sole provider's own policies can mitigate this problem as well; Athena Diagnostics, for example, limits to 20 percent the out-of-pocket expenses for patients whose insurance does not cover the test, and offers free or low-cost testing to some patients. Both patients and clinicians have found, though, that participating in Athena's program, as well as government programs like Medicare, involves a burdensome process that can undermine patient access. The case studies found that in some instances coverage of a test offered by a sole provider was generally more limited than the cumulative coverage offered by multiple providers.

In sum, a patent holder's business conduct is an important factor influencing how widely available a genetic test is. When a patent holder practices broad licensing, a test is generally widely available and available in different forms and at different prices. On the other hand, when a patent holder decides to provide the testing itself without further licensing or to exclusively license to single provider, the test will be available only from that source, and patient access to high-quality genetic testing may suffer.

How did patents and licensing practices affect efforts directed toward improving upon genetic tests?

In cases where there were many licensed providers, efforts at innovation proceeded. On the other hand, where there was a sole provider, such as in the case of the breast/ovarian cancer tests and the test for LQTS, the case studies documented assertions of problems in innovation. The case studies, in particular, highlighted clinicians' allegations that the sole providers responsible for these tests offered tests that were inadequate and that competition would have led to needed test innovations. In the LQTS case study, some clinicians argued that the provider did not innovate upon its test in ways that were possible and desirable, and in the case of breast and ovarian cancer testing, clinicians publicly testified and wrote in the *Journal of the American Medical Association* (*JAMA*) about Myriad's failure to test for rearrangements, insertions, and deletions. As it turned out, Myriad already was working on adding rearrangements, insertions, and deletions to its test, but the appearance of the *JAMA* article may have caused Myriad to accelerate its efforts. In the LQTS case study, the case study authors suggest that, if there was more competition, there might be greater progress in understanding the complicated genetics of LQTS, which in turn would improve testing for the disease.

Sole providers, such as Myriad, Athena Diagnostics, and PGx Health, also have failed to publicly assure would-be innovators that they will not consider certain innovations to be infringing. Without this assurance, would-be innovators may choose not to pursue improvements upon a patented test for fear that they will be sued.

The hearing loss case study reveals that test developers are pursuing innovations that include unpatented and patented genes; it is possible, though, that the relevant patent holders may seek to enjoin the multiplex systems that are being developed.

As the above information suggests, a patent holder's business conduct significantly affects innovation upon the test. When a patent holder chooses to license to others the right to pursue innovations, innovation will likely proceed, although such innovation will

carry the additional cost of a license fee. A patent holder who chooses to practice his or her own invention, without further licensing, can also choose to innovate upon his or her own test, perhaps by adding other relevant and unpatented genetic sequences. Of course, if the patent holder makes incomplete and ineffective changes to the test, then innovation will not occur. A patent holder also could choose not to innovate on his or her own test and not to license it to others. Patent holders also can limit innovation by failing to provide notice that they will not enforce patents against research use or innovations made by others, causing a chilling effect on R&D resulting from fear of patent infringement liability.

What is the potential that the patent may cause some future harm?

The case studies note that patents relating to genetic tests could hinder the anticipated increase in multiplex genetic testing and the foreseeable clinical use of whole genome analysis/sequencing. Multiplex testing involves simultaneous testing for many genes and will likely be the necessary norm as genetic testing accelerates. The various genes needed for a multiplex test, even a multiplex test for a single disease/condition, may be covered by patents spread among various companies and individuals. Therefore, any entity or individual hoping to develop a multiplex test would face the daunting task of having to secure licenses from all of the relevant patent holders—and any patent assignee that refuses to license could derail the development of a comprehensive test.

Similarly, a developer that wished to offer whole genome sequencing would presumably have to obtain licenses for all unexpired patents that claim a nucleic acid molecule derived from the human genome or that claim a diagnostic process that involves a nucleic acid molecule derived from the human genome. To obtain these licenses, the would-be test developers would have to first search the patent database for the relevant genes. Assuming one could identify all relevant patents, the would-be innovator next would need to contact the patent assignees to determine whether a license is available. Although this is a seemingly straightforward task, patent assignees at times are reluctant to respond. There is also the possibility that the person contacted—whether an assignee or licensee

contacted for sublicensing rights—may provide incorrect information; for example, the licensee may incorrectly represent his or her sublicensing rights (as occurred when Smart Genetics obtained a sublicense from Athena Diagnostics that ultimately was determined to be invalid). Moreover, a would-be test developer, for strategic business reasons, might prefer to know the potential availability of a license from a patent holder or sublicense from a licensee without having to contact the assignee or licensee and reveal his or her planned test.

A public database that provides relevant information on patent holders' licenses, as well as information on the patent holders' openness to further licensing and the openness of licensees to sublicensing, would enable would-be innovators to discretely and independently determine their potential ability to develop a noninfringing test. Until such a database is created or an alternative solution is presented, the challenges developers face in determining their legal "freedom to operate" may discourage the development of multiplex tests and whole genome sequencing tests.[288]

Even assuming that a solution is presented to the above problems, the cumulative cost of the multiple licenses needed for a multiplex test or whole genome sequencing might make any proposed test prohibitively expensive. The anticipated cost of these tests may discourage development or limit the marketability of any developed test.

Navigenics, whose Health Compass service provides whole-genome scanning for single nucleotide polymorphisms (SNPs) relating to various health conditions, has proposed that patents on specific, naturally occurring SNPs or other DNA variations used for risk assessments "should be licensed non-exclusively, on commercially reasonable and non-discriminatory terms and according to a royalty model that appropriately reflects the

[288] In practice, some technology developers do not research their freedom to operate before marketing a product. Infringement suits brought against these developers could enjoin them from marketing or impose upon them multiple royalty payments.

relative contribution of the licensed SNP or other DNA variation to the overall value of the service and information provided."[289]

Finally, intellectual property rights and their application are sometimes mentioned as important factors to consider with regard to quality in genetic testing. From the onset of its deliberations, the Task Force believed that patenting and licensing practices may not be the most productive area of focus in trying to improve the quality of genetic tests. Rather, as mentioned previously, issues related to clinical and patient access and quality might be better addressed through the evaluation of the regulation and oversight of genetic tests (especially when the root issue of contention is quality) as well as coverage and reimbursement systems for such services. The Task Force's deliberations in support of this report confirm those initial views. Nevertheless, ensuring quality in genetic testing is a complex matter, and insofar as patents and licensing practices may hinder the development of multiplex tests and whole genome sequencing, they can affect the overall state/quality of genetic testing.

Preliminary Conclusions

Patents and Pricing

Evidence from the case studies did not reveal widespread overpricing for genetic diagnostic tests that were patented and exclusively licensed relative to tests that were either unpatented or non-exclusively licensed. In addition, SACGHS did not find quantitative information in the general literature on this issue nor has it been addressed in international policies.

[289] Navigenics website. "Our policy regarding gene patents," http://www.navigenics.com/visitor/what_we_offer/our_policies/gene_patents/ [accessed January 30, 2009].

Effects of Patents on Access

Thus far, patents covering genetic tests and related licensing practices do not appear to be causing wide or lasting barriers to patient or clinical access. The case studies document several instances in which patient access to genetic tests may have been impeded. For the most part, those cases were resolved and access to those testing services is no longer an issue. In the cases where patient access problems arose, the problems were generally caused not by the patent itself but by the way it was licensed or used. For example, access problems occurred when:

- The sole provider did not offer the test for a period of time.
- The sole provider did not offer complete testing of alleles and rare genes.
- A sole provider did not have a coverage contract with a major payer.

Evidence from the case studies indicates that clinical access can be affected by the use and enforcement of intellectual property rights. Controversies are more likely to occur when the interests of medical practitioners and patients are not taken into consideration during the licensing process, (e.g., genetic testing for Canavan disease; *BRCA* testing).

Patent protection of a genetic test may limit clinical access to a test, but limited clinical access to a test does not always result in limited patient access to a test.

Patenting of a test may limit the ability of multiple labs to offer a test through at least two mechanisms. First, where the test is offered only by the patent holder or only by an exclusive licensee, other laboratories naturally will not be able to offer test. Alternatively, when a test is non-exclusively licensed, some laboratories may not be able to offer it when they cannot afford or are unwilling to pay the royalty associated with the non-exclusive license.

In either of these scenarios—one involving a sole provider, the other involving potentially multiple providers, but with some labs not participating—patient access may be affected.

A sole provider can in theory satisfy all patient demand for a test. However, when there is a sole provider, patient access to a test may be harmed in some situations, including 1) when the sole provider has not been able to secure a coverage contract with a particular payer; 2) when the sole provider does not offer complete testing (and other laboratories have not developed a test that covers remaining alleles or rarer genes).

These harms could also result when non-exclusive licensing is practiced and multiple providers are available but the presence of more providers diminishes the chances that a particular payer will not be covered or that rare alleles and genes will not be tested.

Concerns about the quality and validity of genetic tests may be best addressed by enhancing the oversight system for laboratory developed tests. Gaps in the coverage of genetic tests are probably best addressed through changes in health care financing policies. SACGHS has issued in-depth reports and recommendations to address these issues.

Effects of Patents on Innovation and Development

Patents have a utilitarian function—promoting science—and are not awarded as natural rights under U.S. law. Two principal ways patents are supposed to promote science is through stimulating research and inventive activity and through stimulating investment to commercially develop promising inventions. While there is a longstanding consensus that patents function this way in many arenas, the findings from the Committee's work thus far suggest that they do not serve as powerful incentives for either genetics research in the diagnostic arena or development of genetic tests.

The evidence that patents and exclusive licensing practices provide powerful incentives for the development of genetic tests is not strong. Rather, the findings from the case studies suggest that patents offer minor if any stimulus to the development of genetic diagnostics and are not needed to advance the development of genetic tests for patient care.

- Most academic scientists appear to be principally driven to carry out research not by patents but a mix of motives, including the desire to advance their career and general understanding, develop treatments for disease, and earn the esteem of their colleagues. The main factor driving the development of genetic tests is clinical need.

- The case studies show that those researchers who did not pursue patenting were willing and able to invest in developing genetic tests soon after their discovery, despite the threat that "free riders" could then offer competing testing services.

- Development barriers generally do not appear to pose a significant barrier for bringing new diagnostic tests on-line. When a gene sequence is reported, diagnostic testing quickly arises regardless of patent status to meet clinical need. Only after exclusive licenses appear is the market then “cleared” through enforcement of exclusivity.
- Although patented discoveries described in the case studies were also developed into tests, the fact that unpatented genetic discoveries were routinely developed into clinical genetic tests suggests that patents are not needed for development of these tests.

- If regulatory oversight of genetic tests evolves, requiring some type of costly independent review before marketing, patent protection may be needed for companies to be willing to risk resources in satisfying the regulatory requirements.

Exclusive licenses may be needed in some cases to provide a sufficient incentive to develop an invention, but co-exclusive and other less exclusive licenses can also provide incentives for development when certain market conditions are present.

Future Issues and Needs

Given the trend within medicine towards robust genomic analysis of individuals, in the future it may be difficult to engage in multiplex testing and full genome sequence analysis given that many genes have now been patented.

More information is needed on the patents and licenses associated with genetic tests so that the public can better measure access and so that innovators can determine what rights are available. There should be continued monitoring of the market to determine whether any particular entity or group of entities is consolidating the market for genetic testing by buying relevant patents and clearing out competitors.

The findings and conclusions in this report are preliminary, and SACGHS will await public comment and input before coming to final conclusions about whether changes are needed in Federal laws, policies, or programs to address the issues discussed in this report and, if so, what changes to recommend.

Chapter V

Range of Potential Policy Options for Public Consideration

The Committee has deliberated on the types of policy options that might be considered with regard to patents, licensing, and genetic tests but has not yet come to final conclusions. In this final section, the Committee provides a broad range of options for public consideration. These options do not necessarily correlate with any particular conclusion (as described in the previous chapter) but rather provide a framework within which to gather public input. Input about the need for change, the appropriateness, feasibility, and implications of these particular policy options, as well as any others the public might suggest, is needed before SACGHS will be ready to develop specific recommendations. The Committee will carefully consider public input on these options in developing recommendations to the Secretary. At this stage, neither the Task Force nor the Committee has decided which, if any, of these policy options to support.

1. Advocacy Efforts by Key Stakeholders to Ensure Access

A set of principles and guidance documents should be developed that engage stakeholders in a discussion of issues regarding patenting and licensing strategies for genetic diagnostic tests. Specifically, these documents could facilitate the following:

A. To optimize patient access to genetic tests, stakeholders (e.g., industry, academic institutions, researchers, patients) should work together to develop a code of conduct to encourage broad access to such technologies.

B. In those cases where multiple stakeholders (e.g., academic researchers, industry, and patient organizations) have collaborated to advance the identification of gene mutations and the development of a diagnostic test, those stakeholders should work together in determining whether to seek patent protection and how to

disseminate, utilize, and license such technology in a manner that balances the proportional contributions of the stakeholders.

C. A forum should be established to foster a discussion of technology development strategies among research collaborators (e.g., academic researchers, industry, and patient organizations). Strategies should be pursued that balance protecting the intellectual property rights associated with critical research discoveries and developments— such as genetic diagnostic tests— with ensuring appropriate access to such tests and technologies by those patients with a clinical need and by clinicians administering the test. This forum could occur under the auspices of an existing or newly established advisory body, or a special interagency workgroup, including representatives from the Department of Health and Human Services (HHS), the Department of Commerce, and others.

D. Mechanisms could be developed to promote adherence to the principles reflected in NIH's *Best Practices for the Licensing of Genomic Inventions*[290]*;* the Organisation for Economic Co-Operation and Development (OECD) *Guidelines for Licensing of Genetic Inventions* [291]; and the Association of University Technology Managers (AUTM's) *In the Public Interest: Nine Points to Consider in Licensing University Technology*.[292] Professional organizations involved in intellectual property policy and practice in this area should work together to build on those norms and practices as they relate to gene-based diagnostics by articulating more specific conditions under which exclusive licensing and nonexclusive licensing of uses relevant to genetic testing are appropriate. Professional societies should work cooperatively to forge consensus positions with respect to gene patenting and licensing policies.

[290] See http://ott.od.nih.gov/policy/genomic_invention.html.
[291] See http://www.oecd.org/document/26/0,3343,en_2649_34537_34317658_1_1_1_1,00.html.
[292] *In the Public Interest: Nine Points to Consider in Licensing University Technology* is a set of principles crafted by 12 institutions from across the United States in March 2007 and subsequently endorsed by the Board of Trustees of the Association for University Technology Managers and, as of October 2008, approximately 50 other institutions and organizations.

2. Enhancing Transparency in Patents and Licensing

Relevant Federal agencies should encourage and, when possible, adopt practices that will serve to increase the transparency of intellectual property rights associated with genetic diagnostic tests. Such transparency would allow for uniform assessment and monitoring of the intellectual property landscape in this field and intersecting allied fields that foster interdisciplinary development of next-generation technologies. The following policy options offer potential mechanisms through which such transparency might be achieved:

A. Relevant Federal agencies should encourage holders of patents on genes, genetic tests, and related technologies, including academic institutions and companies, to make information about patent licenses readily available either by making the signed licenses publicly available or by disseminating information about their technology and licensing conditions, including such factors as the type of license, field of use, and the scope of technologies that are available.

B. As a means to enhance public access to information about the licensing of patents related to gene-based diagnostics, NIH should amend its *Best Practices for the Licensing of Genomic Inventions* to encourage licensors and licensees to include in their license contracts a provision that allows each party to disclose information about its licenses (including such factors as type of license, field of use, and scope) in order to encourage data-based next-generation innovation.

C. The Secretary of HHS should seek statutory and regulatory authority to enable the Food and Drug Administration and the Centers for Medicare & Medicaid Services to require DNA-based tests (whether offered as a test kit or a laboratory developed test) to display on product packaging or company/provider websites any issued patent and published patent numbers that the company or provider owns and controls and reasonably believes cover their product or patents licensed by the company/provider in order to market the product.

3. Filling Data Gaps

More data are needed on the landscape of gene patenting and the licensing arrangements that are being used to commercialize genetic tests and related technologies. Additional data collected in a uniform way would enable policymakers to more fully assess whether there are any effects, either positive or negative, of gene patents and licensing strategies on patient access to genetic diagnostic tests. The availability of such data in aggregate form also might encourage more scholarly legal and public policy studies. The following policy options would enhance existing information sources within HHS and the Federal Government as a whole.

A. The Secretary of HHS should establish an advisory board that provides ongoing advice about the public health impact of gene patenting and licensing practices. The board could review new data collected on patient access and assess the extent to which limited or enhanced access is influenced by intellectual property practices. The advisory board also could provide input on the implementation of any future policy changes, including any changes that might emerge as a consequence of this report.

B. In order to assess whether gene patent or licensing arrangements may be positively or negatively affecting patient access to genetic tests, HHS and other appropriate agencies should develop a reporting system, both voluntary and mandatory, as appropriate, to encourage researchers and medical practitioners who order, use, or perform genetic tests to report such effects.

Such a reporting system should include a mechanism through which reports can be verified and evaluated in order to better correlate any access issues with gene patenting or licensing activities, arrangements, and terms. For example, the reports may need to include evidence of any patent enforcement activity, such as a cease and desist letter. It may be prudent to pilot test and evaluate such a system before committing to its full development.

C. The agency selected to collect data should develop uniform systems for data collection and reporting, including database structure, standardized terminology, and integration into current systems, such as the existing iEdison system.[293] Once established, the Secretary of HHS should encourage HHS funding recipients to submit more data about inventions that, at the time they are patented and licensed, are reasonably anticipated to be associated with clinical genetic tests. The data elements that might be most useful include:

1) whether the licensor of the invention granted the licensee the rights to make and sell a clinical genetic test or provide a clinical service;

2) the nature of the licensing agreement (e.g., exclusive, co-exclusive, nonexclusive) and for licenses with some degree of exclusivity in the grant, information about the grant of license rights (i.e., field[s] of use, scope) and whether or not the license has nonfinancial performance incentives (diligence);

3) patent number and patent and licensing timelines (dates of patent filing, publication, issuance, and license effective dates);

4) the date of the first reported sale of a genetic test or service and periodic notations of whether the test or service remains on the market; and

5) some measure of volume of sales (in number of tests or kits sold), even if such sales are not royalty bearing, and the geographic locations of such

[293] Under the Bayh-Dole Act, recipients of Federal grants, cooperative agreements, and contracts are required to report to Federal agencies about inventions that result from federally funded research. Such reports can be submitted through an online information management system called iEdison. The reports are considered proprietary and are not publicly available. Grantees are not required to submit their reports through iEdison. NIH also requires recipients of NIH funding, upon election of title to an invention, to report utilization data annually for that invention, including whether and how many exclusive and nonexclusive licenses have been granted (if any)

sales. The latter could aid in determining whether testing is reaching those in need who might be geographically isolated.

Providers of the data should be consulted about the design of the database, the development of its standard terminology, and their perspectives on the burden and implications of reporting such data.

D. Research agencies (e.g., NIH, the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, and others as recommended) should explore using summary data from their respective Federal funding agreements as a tool for assessing the extent to which licensing practices of identified patents play a role in patient access to diagnostic gene-based inventions. NIH also should explore whether iEdison data could be used to assess whether the licensing of genomic inventions has been conducted in accordance with NIH's *Best Practices for the Licensing of Genomic Inventions*.

4. Federal Efforts to Promote Broad Licensing and Patient Access

The potential implications surrounding the patenting of genes and the licensing of genetic technologies have been the subject of several U.S. and international reports and guidance documents, discussed in Chapter III of this report. Because the public sector frequently looks to the actions of the Federal Government for guidance in addressing such challenging issues, the following policy options are intended to highlight Federal actions that would encourage intellectual property management strategies that foster patient access to genetic tests and technologies.

A. Federal agencies should promote wider adoption of the principles reflected in NIH's *Best Practices for the Licensing of Genomic Inventions* and the OECD *Guidelines for Licensing of Genetic Inventions*, both of which encourage limited use of exclusive licensing for genetic/genomic inventions.

B. Federal agencies should encourage wider use of AUTM's *In the Public Interest: Nine Points to Consider in Licensing University Technology*. Points two and nine are particularly relevant for genetic tests. They state, in part, that "exclusive licenses should be structured in a manner that encourages technology development and use" and that in licensing arrangements, institutions should "consider including provisions that address unmet needs, such as those of neglected patient populations," giving particular attention to improved diagnostics, among other technologies.

C. Federal agencies should explore whether mechanisms such as patent pooling could facilitate the use of rapidly developing technologies for genetic tests that are dependent upon on multiple licenses of patents and what, if any, situations would be amenable to patent pools as an access mechanism.

D. Federal agencies should consider providing more detailed guidance for gene-based clinical diagnostic inventions to encourage patent holders to use terms in licensing agreements, such as due diligence clauses, to foster the availability and utility of clinical diagnostic tests and thereby reduce the likelihood that exclusivity associated with a license would lead to adverse effects on patient access. For example, taking steps likely to increase the number of insurers that reimburse for the test or improving the specificity and sensitivity of the test and enhancing knowledge of its clinical validity are milestones that a licensee could be required to meet to earn or maintain license rights.

5. Licensing Policies Governing Federally Funded Research to Facilitate Access

The Bayh-Dole Act of 1980 was enacted to promote the commercialization of federally funded inventions and resulted in the patenting of many discoveries of biomedical interest. The policy options that follow are intended to ensure that intellectual property rights are applied in a manner that enhances the availability of a genetic test or technology to the public for diagnostic, therapeutic, and other research purposes.

A. NIH should explore the feasibility of making compliance with NIH's *Best Practices for the Licensing of Genomic Inventions* an important consideration in future grants awards.

B. The Secretary of HHS should request an Executive Order clarifying the authority of HHS under the Bayh-Dole Act to ensure that the goals of the statute are being fulfilled in the context of genetic diagnostic tests, in the manner reflected in NIH's *Best Practices for the Licensing of Genomic Inventions*.

C. The Secretary of HHS should request an Executive Order clarifying the authority of HHS under the Bayh-Dole Act to impose on the grantee or contractor a presumption that any inventions resulting from government funding will be licensed nonexclusively when they are licensed for the genetic diagnostic field of use. The presumption, which could be made a term and condition of an award, could be overcome by showing that an exclusive license was more appropriate, given the high costs of developing the test.

D. The Secretary of HHS could promulgate a departmental regulation accomplishing any of the above three policies, if the Secretary or his or her legal counsel determines that such a regulation is consistent with the Bayh-Dole Act.

6. Study Federal Implementation of Intellectual Property Laws

One key finding arising from this study is that information regarding the implementation and downstream effects of Federal intellectual property laws is sparse, particularly with regard to DNA-based inventions. The following policy options are intended to promote continued analysis and evaluation of these laws within this rapidly evolving field.

A. The Secretary of HHS, in collaboration with other relevant departments, should commission a study to evaluate and compare how Federal agencies have managed Government-owned DNA-based inventions with diagnostic fields of use.

B. The Secretary of HHS, in collaboration with other relevant departments, should commission a study of how agencies have interpreted and applied the Bayh-Dole Act with respect to the application of the statute's march-in provisions.[294]

7. Improving and Clarifying U.S. Patent and Trademark Office (USPTO) Policy

The HHS Secretary does not have a direct role in issuing patents. Therefore, the following policy options are directed to the Secretary of Commerce and USPTO.

The Secretary of HHS should recommend that the Secretary of Commerce advise USPTO to:

A. establish an advisory committee to provide advice about scientific and technological developments related to genetic tests and technologies that may inform its examination of patent applications and other proceedings;

B. craft new guidelines for nonobviousness to assist USPTO personnel in examining patent applications on nucleic acids and genetic diagnostics—and particularly those applications seeking patent protection for human DNA sequences and/or genes for diagnostic purposes. The guidelines would be analogous to the Utility Guidelines published in 2001[295]; and

[294] In response to a congressional mandate, GAO is querying NIH, DOD, DOE, and NASA about 1) their policies and procedures to determine whether march-in rights under the Bayh-Dole Act should be exercised; 2) the extent to which these agencies have exercised march-in rights; and 3) any barriers they have encountered in the exercise of march-in rights. The findings of the GAO's inquiry may be relevant.
[295] See USPTO *Guidelines for Examination of Applications for Compliance with the Utility Requirement,* http://www.uspto.gov/web/offices/pac/mpep/documents/2100_2107.htm,

C. develop guidelines on the patentable subject matter in the wake of *In re Bilski* and its progeny.[296]

8. Options Related to Statutory Change

Most of the policy changes outlined above would apply to patents issued to the Federal Government or to scientists funded by the Federal Government. Statutory changes, such as those described below, would apply not only to government-owned and funded inventions but also to those inventions funded by the private sector. As noted before, SACGHS has not concluded that changes of this nature are necessary or appropriate to address patient and clinical access to genetic diagnostics. Rather, before coming to a conclusion about final recommendations, it is vital for the Committee to obtain the public's perspectives regarding the pros and cons of various options. Six statutory options are outlined below (one with three variations); some of these ideas were put forward as legislative proposals in prior sessions of Congress.

A. Make no changes to the law at this time.

B. Prohibit or limit the patenting of diagnostic tests that rely on an association of a particular genotype with a disease/disorder, or provide specific guidance regarding the scope and conditions under which such patents would be appropriate.

C. Modify the Patent Act as necessary to expressly withhold the right of injunctive relief from patent holders or their licensees who are impeding patient access to a genetic diagnostic test, similar to exclusionary provisions that protect medical practitioners.

[296] *In re Bilski*, --- F.3d ----, 88 U.S.P.Q.2d 1385 (Fed. Cir. Oct. 30, 2008).

D. Create an exemption from patent infringement liability for medical practitioners who order, use, or perform diagnostic genetic tests in clinical care. Related health care entities also should be covered by this exemption.

E. Create an exemption from patent infringement liability for those who order, use, or perform diagnostic genetic tests in the pursuit of research. Related health care and research entities also should be covered by this exemption.

F1. Require that patents on human health-related nucleic acid sequences be limited to the utilities specified in the patent.

OR

F2. Prohibit patents on processes that use human health-related nucleic acid sequences for diagnostic purposes.

OR

F3. Prohibit patents on human health-related nucleic acid sequences.

Chapter VI

Summary

To be written following the public comment period.